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VASCULAR PATTERN OF LESIONS OF MULTIPLE SCLEROSIS

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The theory of a relation between the cerebrovascular system and the lesions of multiple sclerosis has been advanced by many workers. The first of many to assign a primary role to vascular lesions was Rindfleisch.[1] Ribbert [2] early maintained that the demyelinated areas were related to a primary disseminated thrombosis. He described a congested central vessel in all the sclerotic patches. In two small patches cut in serial section he found white blood cells in the lumen of the vessel, partly adherent to the vessel wall and partly filling the vessel as an embolus. He stated that these changes in the vessel were multiple thrombi and expressed the belief that they had an important causative role in multiple sclerosis. The most recent adherents to the idea that vascular lesions play a primary role in the pathogenesis of the lesions of multiple sclerosis have been Putnam and his collaborators.[3]

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Dawson [4] and Symonds,[5] although recognizing a frequent relation between the lesions and small vessels and even observing pathologic changes in the vessels, including occasional thrombi, expressed the belief that these changes were secondary to "inflammation" produced either by the noxious agent or by the breakdown of the damaged tissue. In this opinion they were in accord with a host of earlier workers, and Wilson [6] seemed to adhere to this view.

Other investigators look on this disease as either a primary involvement of glial tissue or, as most recently affirmed by Hassin,[7] a degenerative disease of myelin sheaths independent of the vascular supply.

No one has as yet furnished an analysis of a sufficiently large number of lesions studied with serial sections to allow a quantitative estimate of the incidence of the association of vessels and lesions and the frequency with which thrombi may be found. Serial section studies were mentioned by Ribbert,[2] Falkiewicz,[8] Anton and Wohlwill,[9] Daw-

Med. **9**:854-863, 1936; (*f*) Studies in Multiple Sclerosis: VII. Similarities Between Some Forms of "Encephalomyelitis" and Multiple Sclerosis, Arch. Neurol. & Psychiat. **35**:1289-1308 (June) 1936; (*g*) Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," ibid. **37**:1298-1321 (June) 1937. (*h*) Putnam, T. J., and Adler, A.: Vascular Architecture of the Lesions of Multiple Sclerosis, ibid. **38**:1-15 (July) 1937. (*i*) Putnam, T. J.: Lesions of "Encephalomyelitis" and Multiple Sclerosis: Venous Thrombosis as the Primary Alteration, J. A. M. A. **108**:1477-1480 (May 1) 1937. (*j*) Hoefer, P. F. A.; Putnam, T. J., and Gray, M. G.: Experimental "Encephalitis" Produced by Intravenous Injection of Various Coagulants, Arch. Neurol. & Psychiat. **39**:799-812 (April) 1938. (*k*) Putnam, T. J., and Alexander, L.: Tissue Damage Resulting from Disease of Cerebral Blood Vessels, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:544-567, 1938. (*l*) Alexander, L., and Putnam, T. J.: Pathological Alterations in Cerebral Vascular Patterns, ibid. **18**:471-543, 1938. (*m*) Putnam, T. J., and Alexander, L.: Disseminated Encephalomyelitis: Histologic Syndrome Associated with Thrombosis of Small Cerebral Vessels, Arch. Neurol. & Psychiat. **41**:1087-1110 (June) 1939. (*n*) Putnam, T. J.: Abnormalities of the Blood Associated with "Encephalomyelitis" and Multiple Sclerosis, ibid. **45**:725-729 (April) 1941.

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9. Anton, G., and Wohlwill, F.: Multiple nicht eitrige Encephalomyelitis und multiple Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **12**:31, 1912; cited by Putnam and Adler.[3h]

son [4] and Putnam,[3] but no large group of lesions has been analyzed by any previous worker. In an effort to throw more light on this controversial problem, a study of complete serial sections through 60 lesions in 5 cases of multiple sclerosis is reported. The importance of deciding this issue is apparent, for as a result of the emphasis recently placed on vascular factors the unfortunate patients with this disease are already being subjected to surgical procedures in an effort to improve the circulation of the brain—for example, the series recently reported on by Koch and de Savitsch [10] in an article entitled "Surgical Treatment of Disseminated Sclerosis by Sympathectomy and Ganglionectomy."

MATERIAL

All 5 of the cases studied were typical examples of multiple sclerosis from a pathologic standpoint. In 4 cases the clinical course was in every way characteristic of the disease. In the case of Geerts a more fulminating course than is usually seen obscured the true nature of the process. A detailed summary of the clinical findings in this case as well as a report of the pathologic observations in all 5 cases follows.

CASE 1 (Geerts).—A woman aged 38 was examined by Dr. L. van Bogaert on Dec. 11, 1934. In 1930 she had fallen in a stairway, after which she had pain in the back. Six months prior to the time of examination she had undergone a definite change of personality. Three weeks before the examination she suffered from severe vertigo and a few days later fell backward. At this time she vomited frequently and complained of severe pain in the back and limbs.

Examination revealed the patient to be prostrated with incessant vomiting. There was flaccid paraplegia, with abolition of tactile, pain and deep sensation up to the level of the twelfth dorsal to the first lumbar segment. The plantar and abdominal reflexes were absent, and the achilles and patellar reflexes were greatly diminished. There was incontinence of the vesical sphincter. The reflexes were equal and active in the upper limbs. There was marked nystagmus. The pupils were miotic and reacted normally to light and in convergence. The eyegrounds were normal. Examination of the spinal fluid showed 20 cells per cubic millimeter, 220 mg. of total protein per hundred cubic centimeters and a strongly positive Pandy reaction. On December 18 stiffness of the neck, complete paralysis of the right arm, weakness of the left arm and difficulty with swallowing were noted. The patient died on December 22. Because of the peculiar evolution of the disease during the short period of observation, the diagnosis of multiple sclerosis was not made.

Postmortem Examination (Dr. H. J. Scherer).—Anatomic Description of the Brain: The brain was fixed in solution of formaldehyde U. S. P. and sectioned grossly. The meninges and basal vessels showed no changes. The cut sections revealed a certain hyperemia of the white substance. Inspection revealed plaques, generally round, nicely limited and about the size of a pea. Some of them involved the cortex alone; others were limited to the U fibers and here formed a half-moon–

10. Koch, C. F., and de Savitsch, E.: Surgical Treatment of Disseminated Sclerosis by Sympathectomy and Ganglionectomy: Technique by the Anterior Approach, Brit. M. J. **1**:1254-1258, 1938.

shaped lesion along the boundary between the gray and the white matter. Almost no lesions occurred in the deep white substance. There was predilection of the spots in the brain substance for the area about the lateral ventricles. The plaques were often gray, but more often pink. Similar lesions were observed in the pons, the medulla and the cerebellum.

Anatomic Diagnosis.—The diagnosis was multiple sclerosis, of relatively acute type.

Case 2 (André).—The case of this patient, who had been ill for five years, was a classic instance of multiple sclerosis, fulfilling all the criteria of the disease, and was diagnosed by Dr. L. van Bogaert as one of multiple sclerosis.

Postmortem Examination (Dr. H. J. Scherer).—Anatomic Description of the Brain: The entire brain and spinal cord were fixed in solution of formaldehyde. The basilar vessels showed no lesions. The frontal convolutions were slightly atrophic. The meninges presented a slight whitish thickening over the two fronto-parietal convexities. In sections cut in the frontal plane one found at all levels small gray, discretely limited lesions the area of which was variable but generally smaller than a lentil. The lesions were sparse but were most frequently seen in the frontal sections about the ventricles and immediately under the cortex. Lesions of the same quality, but more extensive, were seen about the occipital horns. In places the gray lesions took on the character of a thin, concentric periventricular ribbon. At the level of the thalamus some tiny lesions were noticed. In the medulla there was a zone of demyelination about the fourth ventricle. The cerebellum was almost completely spared.

Anatomic Diagnosis.—The diagnosis was typical multiple sclerosis.

Case 3 (Sel).—The clinical findings in this case are to be reported elsewhere by Drs. Borremous and van Bogaert. The disease began at the age of 35 years and ran a course of six years. The clinical diagnosis was multiple sclerosis.

Postmortem Examination (Dr. H. J. Scherer).—Anatomic Description of the Brain: The entire brain was fixed in solution of formaldehyde and sectioned horizontally. Very extensive symmetric periventricular demyelination, especially in the occipital and parietal lobes, and equally small grayish plaques in all parts of the centrum ovale, as well as in the white matter of the cerebellum, were noted. In the temporal lobes the demyelination occurred also in the axial part of the white matter. Here only the U fibers seemed intact. There was intense gliosis of the external capsule and the white substance of the insula. The changes were not obvious in the region of the third ventricle. The corpus callosum seemed little shrunken, and the plaques were not frequent. The basilar parts of the pallium showed tiny cystic lesions. There were no changes in the meninges or vessels. The ventricles were not enlarged. The spinal cord and peripheral nerves were not examined.

Anatomic Diagnosis.—The diagnosis was multiple sclerosis, with symmetric diffuse periventricular demyelination.

Case 4 (Depris).—This case was a classic instance of multiple sclerosis, fulfilling all criteria of the disease. The onset was at 31 years of age, and the illness ran a course of eight years. The clinical diagnosis by Dr. L. van Bogaert was multiple sclerosis.

Postmortem Examination (Dr. H. J. Scherer).—Anatomic Description of the Brain: The brain was fixed in solution of formaldehyde. The meninges presented no abnormality. The frontal lobes showed moderate atrophy of their convolutions. The basal vessels were soft and not thickened. Sections of frontal lobes showed the

lesions were numerous, especially in the subcortical regions and in the white matter of the convolutions, while the neighborhood of the ventricles showed very few lesions. A large lesion had destroyed the whole region of the right dentate nucleus. Some large lesions were found in the thalamus bilaterally. The ventricles were not enlarged. The spinal cord was badly damaged, and multiple lesions were recognized at various levels.

Anatomic Diagnosis.—The diagnosis was multiple sclerosis.

CASE 5 (Urbain).—In this case early mental changes were associated with the onset of the disease, coincident with an acute infection. There was progressive mental deterioration, with eventual complete disorientation in space and partial disorientation in time. The patient also showed all the classic neurologic signs of multiple sclerosis. The disease ran a course of six years, beginning at the age of 25 years. The clinical diagnosis by Dr. L. van Bogaert was multiple sclerosis.

Postmortem Examination (Dr. H. J. Scherer).—Anatomic Description of the Brain: The entire brain was fixed in solution of formaldehyde. The meninges and basilar vessels showed no changes. In the frontal sections small gray plaques were present in all parts of the cerebral white matter, being especially pronounced about the ventricles, where they formed a large periventricular stripe. The cerebellum and medulla were also very rich in lesions.

Anatomic Diagnosis.—The diagnosis was typical multiple sclerosis, with extensive periventricular lesions.

METHOD

Histologic examination of all the cases by the Nissl, Pal-Weigert, Bielschowsky and Holzer technics confirmed in every instance the anatomic diagnosis of multiple sclerosis. For the serial sections a dark Van Gieson stain was found very suitable for showing the outline of the lesions as well as the vascular structures in pyroxylin-embedded material. In some series every section, in most series every other section and in a few series every fifth section was mounted. In all cases it was possible to follow even the smallest vessels from one section to the next. Each section throughout the series for each lesion was enlarged and drawn on translucent paper with the use of an Edinger projection apparatus.

Orthographic projections of the drawings of the individual sections were reconstructed for most of the lesions. In a given transverse section two planes (*A* and *B*, fig. 1), perpendicular to each other and to the plane of the section, were passed through an arbitrary point within the lesion. Points of intersection of these planes with the borders of the lesion and the vessel walls were plotted on graph paper for each of the serial transverse sections. If, in a given section, the vessel was not cut by one of the intersecting planes, points corresponding to the position and diameter of the vessel were projected to the intersecting plane and these readings used in reconstructing the lesion and its vessel. This offers a satisfactory method for visualizing, in three plane diagrams, the course of the vessel as it traverses the lesion plaque. The projection of the vessel when it lay outside the true plane of the diagram was frequently represented by an interrupted line, rather than a solid line, connecting the projection points.

Care was taken to maintain the proper magnification in all diameters of the reconstruction. To obtain alinement of the serial sections at least three relatively fixed structures were chosen. Large vessels in tissues adjacent to the lesion, boundaries between the cortex and the white matter and meningeal surfaces served as fixed points. As each section was enlarged and drawn, the fixed points were alined with those drawn from the enlargement of the preceding section. The

orthographic projections of the sectional views thus reconstructed were made at enlargements of 25 or 50, depending on the size of the lesion. A blotting paper model of a part of the basal nuclei in case 5 (Urbain) was made. In some series intermediate sections were stained with the Nissl technic to assist in the identification of cellular elements. A few blocks were stained with the Masson technic, but in our hands the Van Gieson stain was by far the most useful. A preliminary survey of a case of thrombosis of the longitudinal sinus and of postvaccinal encephalomyelitis was made. The lesions, however, were so different from those of multiple sclerosis as to make comparison unfeasible.

RESULTS

An analysis of the 60 lesions in respect to location, size and shape, both for the whole group and for plaques from the individual cases, is shown in table 1. It will be noted that over half the lesions were

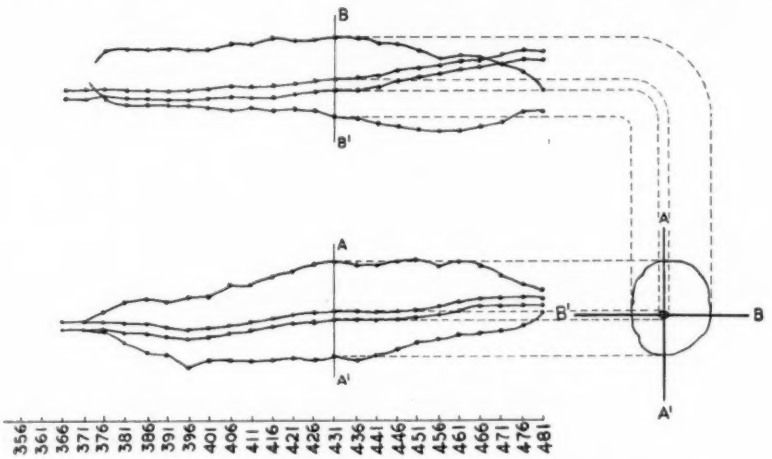

Fig. 1.—Orthographic projection of a cylindric lesion with a vessel passing through it along its long axis.

TABLE 1.—*Location, Size and Shape of Lesions for the Total Group and for the Individual Cases*

Individual Case	Total Number of Lesions Studied	Location of Lesion			Size of Lesion			Shape of Lesion				
		Gray Matter	White Matter	Mixed Gray and White Matter	Less Than 2 Mm.	2 to 3 Mm.	Over 3 Mm.	Spherical	Ellipsoid	Cylindric	Crescentic	Irregular
Geerts	2	1	1	0	0	1	1	0	2	0	0	0
André	2	0	1	1	1	0	1	0	1	1	0	0
Sel	5	0	5	0	2	1	2	0	4	0	0	1
Depris	19	1	10	8	7	6	6	2	7	7	1	2
Urbain	32	1	12	19	25	5	2	8	17	3	2	2
Total	60	3	29	28	35	13	12	10	31	11	3	5

from a single case, that of Urbain. It so happened that most of these lesions were from a single series through the brain stem in the mesencephalic and diencephalic regions. In this series an unusually large

TABLE 2.—*Presence or Absence and Type of Vessel in the Total Group of Lesions and in Individual Cases*

	Total No. of Lesions Studied	Central Vein Absent	Normal-Appearing Vein	Collapsed Central Vein	Distended Vein	Thrombus Formation
Geerts	2	1	1	0	0	0
André	2	1	1	0	0	0
Sel	5	2	2	0	1	0
Depris	19	5	5	0	4	5
Urbain	32	11	11	2	4	4
Total	60	20	20	2	9	9

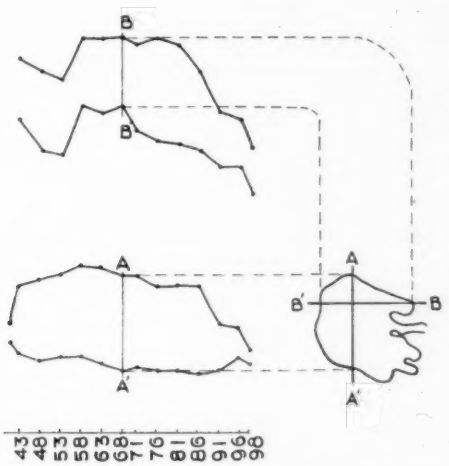

Fig. 2.—Orthographic projection of an irregularly shaped lesion having no vessel larger than a capillary within its borders.

number of small lesions was found. This accounts in the case of Urbain, for the disproportionately large number of lesions in the group occurring in mixed gray and white matter, as well as in the group under 2 mm. in largest diameter. When all 5 cases were taken together, lesions were studied from the cerebral cortex, the subcortical white matter, the corona radiata, the internal capsule, the basal ganglia and midbrain, the optic tract, the cerebellum and the spinal cord. As blocks from corresponding regions were not always available in each case, there was some difference in the parts of the brain studied in the various cases. When the location of the lesions was correlated with their shape it was found that the 3 crescentic lesions were all located in the subcortical white matter and the adjacent cortex. Aside from

this association of location and shape, there did not seem to be any one part of the nervous system in which the lesions tended to have a particular shape. For example, the 11 cylindric lesions were scattered among all possible sites except the cerebellum. As can be seen from table 1, over two thirds of the total number of lesions were definitely elongated, there being 31 ellipsoid and 11 cylindric lesions. Aside from a slightly greater number of cylindric lesions in the case of Depris than might be expected, the case distribution could be entirely explained on a chance basis.

The relation of the vascular system to the lesions may be seen in table 2. It will be noted that by chance exactly one third, or 20, of the lesions were classified as those with the "central vein absent." In 14 of these no vein whatever could be found. Figures 2 and 3 illustrate such a lesion. The lesion might contain a vessel of capillary size, but neither a vein nor any sign of an old obliterated venous channel could be found. In the remaining 6 lesions in this group multiple small venous channels were seen. They could not be classed as central, but apparently were fortuitously included in the sclerotic plaque. There were 4 lesions with multiple veins which were so oriented as to be considered truly central. The 40 lesions in which a central vein was found were further subdivided into lesions the veins of which were normal, collapsed, distended or thrombosed. It is of interest that in no lesion could it be said that there was a central artery. To be sure, small arteries might be seen in the larger lesions. The central vessel could in all cases be identified as a vein by tracing it to its union with a large unmistakable venous channel. All veins were traced for considerable distances central and peripheral to the lesion. In 20 lesions the vein appeared to be perfectly normal (fig. 4), in 2 lesions it was collapsed and in 9 it was distended. In the remaining 9 lesions definite occlusions were found which we have interpreted as being due to venous thrombosis. These occlusive changes consisted of complete filling of the vascular channel by a plug of mononuclear cells of various types, and in a few instances a segment of the vein was replaced by a cord of fibrous tissue. There was proliferation of the endothelium and occasionally necrosis of the vessel wall. The vessel central to the occlusion was collapsed, and peripherally it was dilated. Immediately distal to the occlusion there was freshly clotted blood, with broken-down blood corpuscles and strands of fibrin. This in turn gave way to a segment of the vessel which was distended and packed with normal-appearing red blood corpuscles. Putnam and his associates have laid considerable stress on the statement of Kusama [11] that thrombi in small veins may

11. Kusama, S.: Ueber Aufbau und Entstehung der toxischen Thrombose und deren Bedeutung, Beitr. z. path. Anat. u. z. allg. Path. **55**:459-544, 1913.

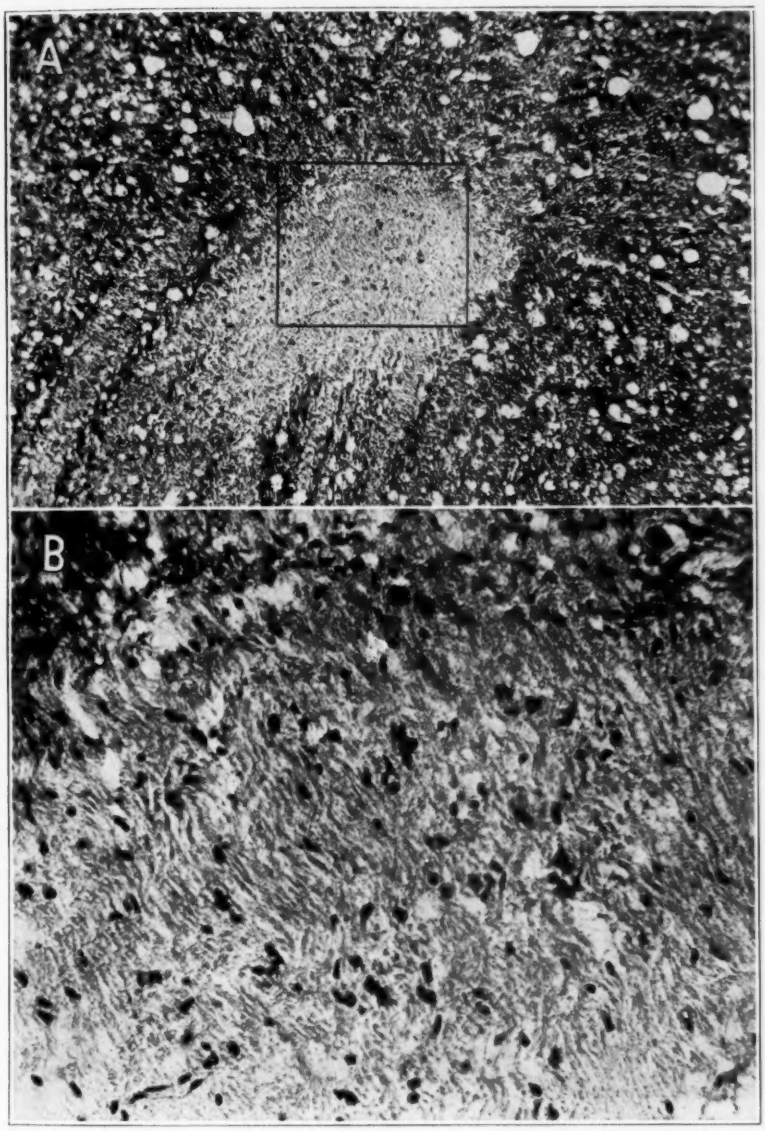

Fig. 3.—Photomicrograph of a section from the lesion shown diagrammatically in figure 2. *A*, low magnification, and *B*, high magnification.

disappear completely, without leaving a trace. It seems to us that a statement such as that by Putnam,[3c] "A thrombus in a small vessel may become so completely organized as to be unrecognizable within a week,"

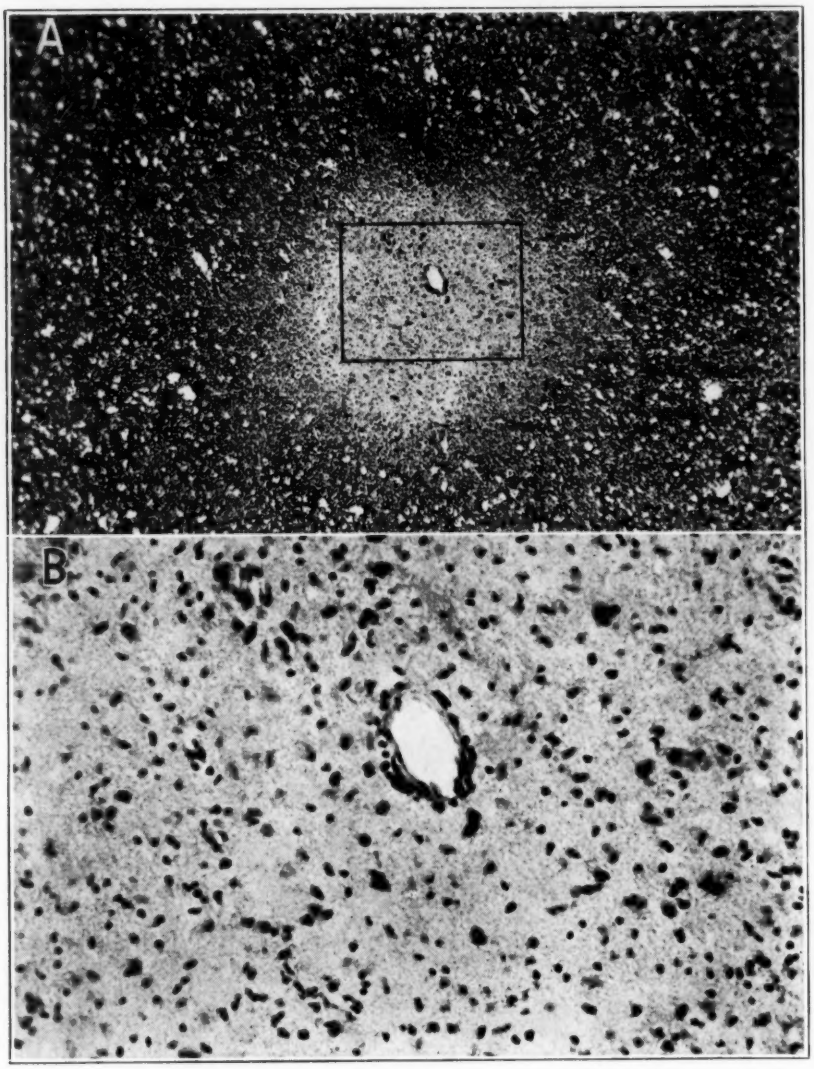

Fig. 4.—Photomicrograph of a section from the lesion shown diagrammatically in figure 1. *A*, low magnification, and *B*, high magnification.

is difficult to prove. Speaking again of the ultimate vascular changes resulting from thrombi in small veins, Putnam stated:[3g] "The vessel may disintegrate entirely, leaving a collection of fibers and leukocytes

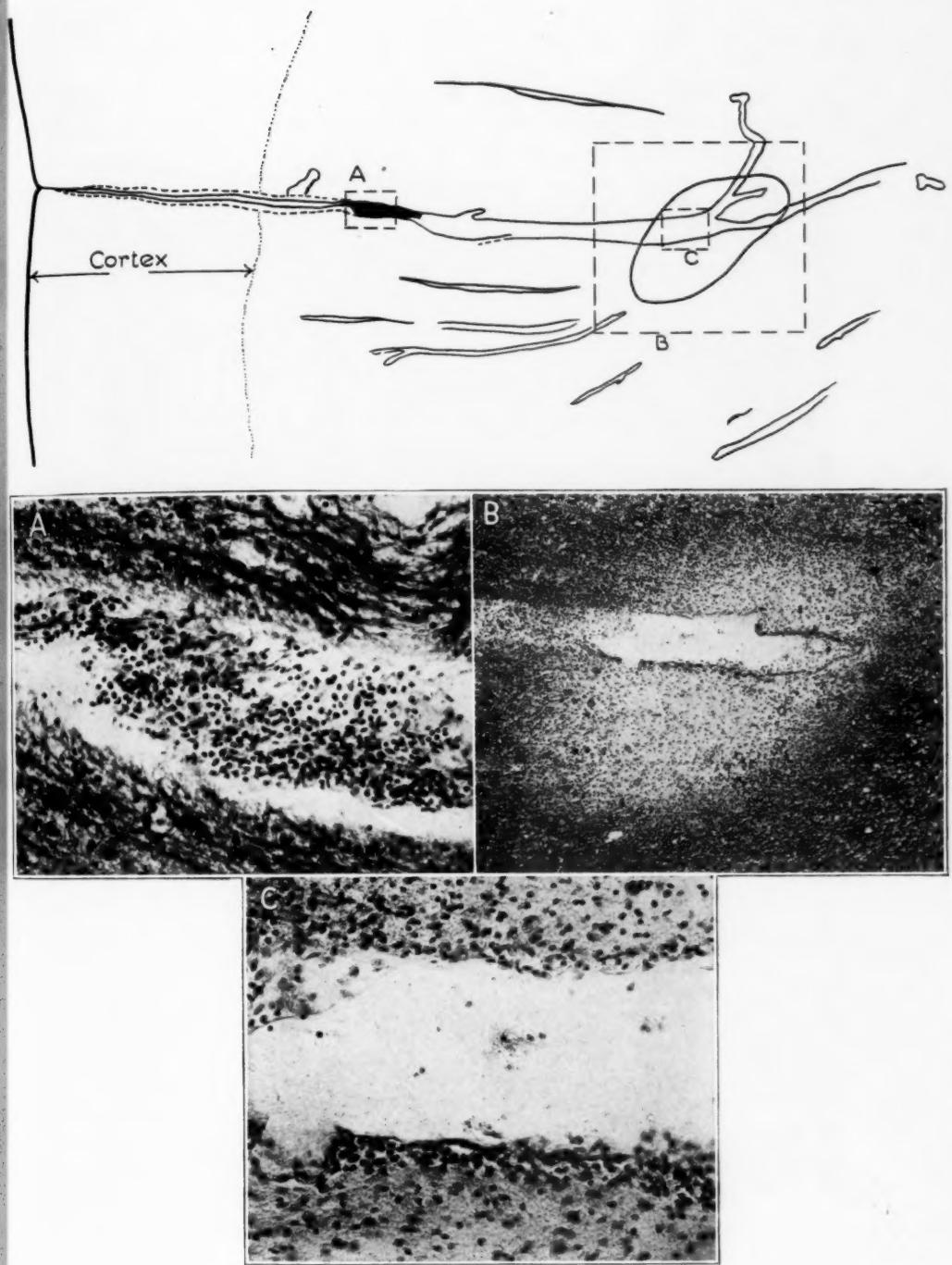

Fig. 5.—A lesion with a central vein thrombosed outside the lesion.

The diagram was made from the composite tracings through several sections to show the topical relations of vein, thrombus and lesion. *B* is a high power photomicrograph through the thrombus; *C* shows the lesion proper under low magnification, and *D*, the central vein dilated and packed with red blood cells in which one sees occasionally areas of freshly formed fibrin.

behind, or the endothelial obstruction may become gradually transformed into a fibrous plug." We are unable to tell exactly what Putnam and his collaborators consider to be the fate of the thrombosed veins in

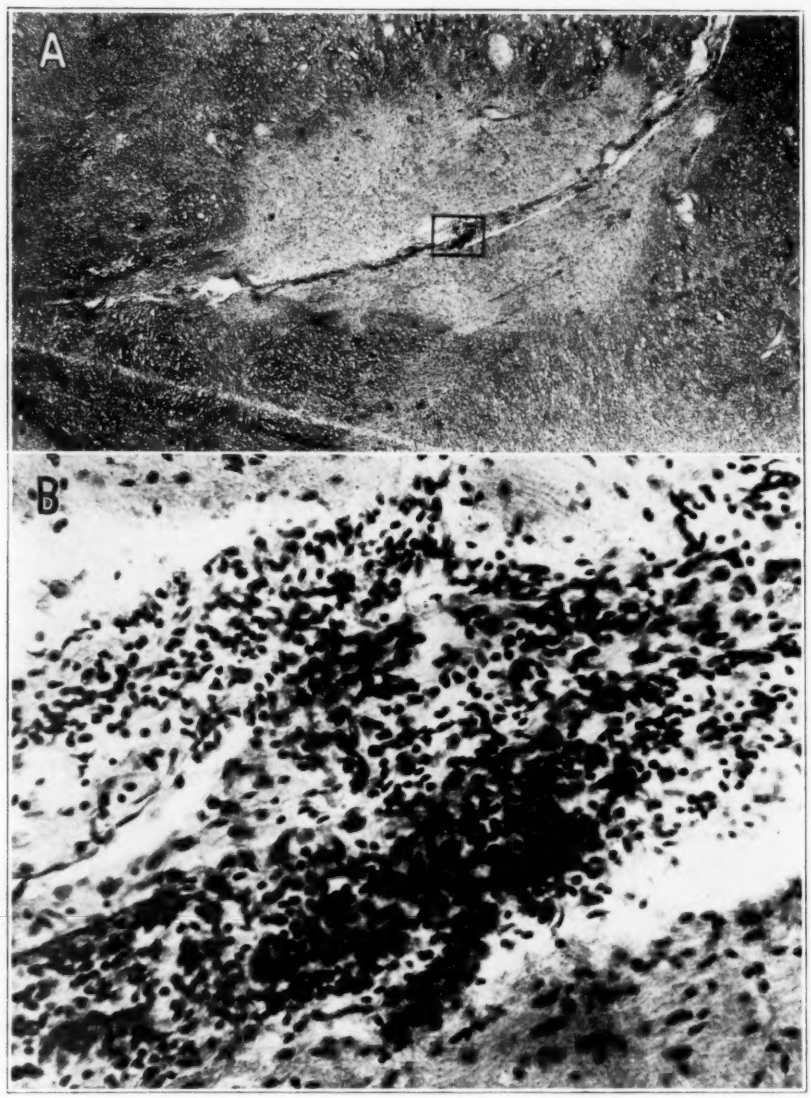

Fig. 6.—A large lesion with a thrombosed central vein cut longitudinally. *A*, low magnification, and *B*, high magnification.

multiple sclerosis. We believe that the changes we have seen would leave a permanent scar in the tissues and that the fibrous cord could be

recognized in serial sections as an obliterated vein. The occlusions which we have observed have every appearance of being of considerable duration. As we shall see later, we do not feel that the thrombi are more frequent in more recent lesions. Of the 9 said to contain a thrombosed vein, in 2 the presence of a thrombus must be admitted to be questionable. In these cases the veins were cut longitudinally and the essential sections happened not to be mounted. The presence of definite distention of the vein distally and a collapsed wall proximally made the existence of an occlusion likely, and the missing sections probably contained the thrombus. In 3 of the 9 cases the site of the venous occlusion was at a considerable distance from the lesion, the

TABLE 3.—*Comparison as to Location, Perivascular Inflammation and Vascular Changes of Forty Veins About Which No Lesion Was Found and Twenty-Five Veins Selected at Random in Apparently Normal Tissue*

	Veins Selected at Random		Central Veins of Lesions	
	Number	Percentage	Number	Percentage
Perivascular round cell response				
Negative	19	76	15	37
Positive	6	24	25	63
Total	25	100	40	100
Condition of vessel				
Collapsed	0	0	2	5
Distended	3	12	9	22.5
Occluded	0	0	9	22.5
Normal	22	88	20	50
Total	25	100	40	100
Location				
Gray matter	0	0	0	0
White matter	18	72	22	55
Mixed gray and white matter	7	28	18	45
Total	25	100	40	100

central vein within the lesion showing only dilatation (fig. 5). In 3 lesions the thrombosed part of the vein was partly within the lesion and partly outside it in perfectly normal-appearing tissue. In only 3 of the 60 lesions studied were the thrombi in the central vein wholly within the lesion. Figure 6 shows one of these lesions in a fortunate section cut longitudinally through the vein. So far as the numbers of individual cases would allow one to say, there seemed to be no difference between the various cases in respect to the frequency of vascular lesions.

It seemed of interest to see whether thrombosis occurred more frequently in the veins which passed through lesions than in veins selected at random and traced throughout their course in normal-appearing tissue. Table 3 shows the two sets of veins compared as to the perivascular cellular response, the condition and the location of the vein. Twenty-five veins were selected at random for this comparison. They

were located in white, in gray and in mixed white and gray matter, just as were the 40 vessels in the lesions. The veins of the two groups had the same diameter and length. It will be seen that the presence or absence of perivascular cells was not restricted to either group. However, the two groups were decidedly different in the percentage showing perivascular cellular infiltration. Only 6 out of 25, or 24 per cent, of the group of veins selected at random showed a perivascular collar, while 25 out of 40, or 63 per cent, of the group showed this cellular reaction. Even more striking was the presence of thrombi in the two groups. Whereas 9, or 22.5 per cent, of the veins in lesions had occlusions, none of the veins selected at random had thrombi. Distended veins were occasionally observed in the first group, but not as frequently as in the veins which passed through lesions. In other words, perivascular cellular reaction and pathologic central veins are more

TABLE 4.—*Correlation Between Presence or Absence and Condition of the Vessel and the Size and Location of the Lesion*

	Total Number of Lesions	Size of Lesion			Location of Lesion		
		Less Than 2 Mm.	2-3 Mm.	Greater Than 3 Mm.	Gray Matter	White Matter	Mixed Gray and White Matter
Central vein absent	20	14	3	3	3	7	10
Central vein present but no thrombus	31	15	9	7	0	17	14
Central vein present with evidence of thrombosis	9	6	1	2	0	5	4
Total	60	35	13	12	3	29	28

common among veins which pass through lesions than in veins which do not.

It was thought that a case of thrombosis of the longitudinal sinus might be useful for comparison with the lesions of multiple sclerosis. It was not possible to demonstrate any perivenous demyelination which remotely resembled the lesions of multiple sclerosis. In this observation we are in accord with Hassin.[12] Table 4 shows the relation between the size and location of the lesions and the absence or presence of veins. It is evident that the distribution of the lesions does not indicate any particular relation between the presence or condition of the vessel and the size or location of the lesion. One notes in table 5 that, aside from the small group of irregular-shaped lesions in which for some unknown reason there was a disproportionate number without a central vein, there was no correlation between the presence or absence of a central vein and the shape of the lesion. If, however, a central vein was

12. Hassin, G. B.: Abscess and Thrombosis of Superior Longitudinal Sinus, Arch. Neurol. & Psychiat. **29**:359-367 (Feb.) 1933.

found in an ellipsoid or a cylindric lesion, it was almost certain to be seen extending along the long axis of the lesion. An example of such a lesion is shown in the orthographic projection of a cylindric lesion (fig. 1). The photomicrograph of the same lesion is shown in figure 4.

An attempt was made to compare the lesions with each other in respect to the degree of various changes found in the plaque. Among these were the perivascular cellular response about the central vein, the

TABLE 5.—*Correlation Between Presence or Absence of Vein and Shape of Lesion*

	Total No. of Lesions	Shape of Lesion				
		Spherical	Ellipsoid	Cylindric	Crescentic	Irregular
Central vein absent	20	2	11	3	0	4
Central vein present, not in long axis of lesion	40	8	2	0	2	1
Central vein present, in long axis of lesion			18	8	1	
Total	60	10	31	11	3	5

TABLE 6.—*Correlation Between Lesions Showing Nonoccluded and Those Showing Thrombosed Veins with Respect to the Intensity of the Perivascular Cellular Reaction, the Degree of Demyelination and the Phagocytic Cellular Response*

	Perivascular Cellular Response About Central Vein			Degree of Demyelination			Phagocytic Cellular Reaction		
		Thrombotic Lesions			Thrombotic Lesions			Thrombotic Lesions	
Degree of Change	Total Number of Lesions	Thrombus In Lesion	Thrombus Outside Lesion	Total Number of Lesions	Thrombus In Lesion	Thrombus Outside Lesion	Total Number of Lesions	Thrombus In Lesion	Thrombus Outside Lesion
0	15	0	3	..	..	..	5	0	0
+	14	0	0	4	0	0	26	3	0
++	6	3	0	13	1	1	17	1	2
+++	5	3	0	32	3	2	12	2	1
++++	..	..	..	11	2	0	..	..	..
Total	40	9		60	9		60	9	

degree of demyelination and the phagocytic cellular reaction. The last two changes might be considered to indicate the age of the lesion. Table 6 shows this evaluation for the whole group and for the 9 lesions the central veins of which had thrombi. The smaller group was then subdivided into the 3 lesions with the thrombus outside the plaque and the 6 with the thrombus partly or wholly within the plaque. It will be noticed that only in respect to the perivascular response was there any essential difference between the group of thrombic lesions and the group as a whole. In other words, with respect to the degree of demyelination or the phagocytic cellular reaction, which we felt might be indicative of

the recent origin of the lesion, the 9 thrombotic lesions fell just about where one might expect they would if there was no relation between the recentness of the lesion and the presence of the thrombus. In respect to the perivascular response, however, all 6, or 100 per cent, of the lesions with thrombi within them showed a 2 or 3 plus cellular reaction, whereas among the 40 lesions with central veins, the group with a cellular reaction 2 and 3 plus included only 11 lesions, or 28 per cent. In other words, there is a positive correlation between the presence of a thrombus in the lesion and a strong perivascular cellular response in the lesion. This correlation might be explained in one of three ways: The thrombus may have caused the more intense cellular reaction; the presence of the cellular infiltration may have resulted in the thrombosis, or the two processes may have shared a common causative agent. The correlation seems too strong to admit pure coincidence. Although one cannot deny the possibility that the presence of the thrombus, with its effects on the vessel, may not be a factor, the fact that almost an equal number of lesions without thrombi were rated as having just as intense a cellular reaction seems strong evidence against this being the only factor. It seems impossible to say which of the other two possibilities is correct. On the basis of what data we have either explanation seems equally good. It might be mentioned in passing that extracts of brain tissue when injected into the blood stream are potent thromboplastic substances. It seems possible that the rapidity of the breakdown of myelin was greatest in the lesions showing the greatest perivascular cellular reaction and that the absorption of the lipoid fractions into the blood stream locally resulted in the formation of the clot at this site rather than in the lesions where the demyelinating process was less rapid.

COMMENT

It seems that the analysis of this series of lesions makes untenable the views of both Hassin[7] and Putnam.[3] Although the lesions were not always oriented about veins, we have found that two thirds of them were. Of interest, too, is the fact that in elongated lesions with central veins the lesions tended in almost all instances to be oriented about the vein like an elongated collar. This seems to indicate that, whatever proves to be the causative agent in this disease, either the tissues about the veins are more susceptible to it or it is concentrated in its effect at this site. Even if, in the light of this study, one were to assume with Hassin[7] that the disease is a diffuse degenerative process, it seems certain that the degeneration occurs more rapidly and more completely about veins.

The presence of pathologic changes in the veins which pass through lesions, particularly occlusions, is worthy of comment. It was shown

that when a fairly large series of veins selected at random from the same cases, in the same parts of the nervous system and of the same size, were compared with the series of veins which passed through lesions in their course, significant differences in the two series appeared. In the one no thrombosed vessels were found, and in the other 9 out of 40 were occluded. If one might assume that thrombi in small veins are only transitory, disappearing without trace, it is conceivable that the thrombus might be a causative factor in the pathogenesis of the process. It does not seem that there is any basis for such an assumption. In fact, we are of the opinion that the changes in the vessels we have studied were not temporary but would leave their mark indefinitely in the tissues. On the assumption that thrombi in small veins are not essentially different from other pathologic processes—that is, when tissue is destroyed a scar is formed—one cannot with logic assign a causative role to the thrombi found in cases of multiple sclerosis. Fifty-one of a total of 60 lesions studied showed no evidence of either recent or old thrombosis. To this must be added the fact that of the thrombi seen only a small minority were restricted exclusively to the lesion. If the thrombus is not the cause of the lesion plaque, do the two share a common origin or is the lesion itself the cause of the thrombosis? We are unable to answer this important question. We are inclined to attribute the thrombosis to the absorption of the thromboplastic substances locally in the lesion. The more intense the breakdown, the more rapid is the absorption and the greater the possibility of the blood clotting. This tentative hypothesis would explain the fact that the thrombus was in every case central to the lesion, that is, in the direction of the blood flow; it would explain the fact that the more intense the process, as measured by the perivascular cellular reaction, the more liable one was to find a thrombus; it might explain the changes in clotting time in cases of multiple sclerosis (Simon and Solomon [13]) and it would not necessitate an agent which had both thromboplastic and myelinolytic properties. It is of interest that extracts of brain tissue are among the most potent agents for production of intravascular clotting. We are unable to explain the fact that in 3 of the 9 thrombotic veins the thrombus was completely outside the confines of the lesion. If our suggestion is correct, namely, that the thrombus is the result of absorption locally into the vein of thromboplastic material, one would expect this to be most concentrated at the site of the lesion. Also against this suggestion is the inability of Putnam to find thrombi in veins adjacent to softenings where there is also a rapid breakdown of brain substance. We are in accord with the view expressed by Dawson,[4]

13. Simon, B., and Solomon, P.: Multiple Sclerosis: Effect of Typhoid Vaccine and of Epinephrine on Coagulation of the Blood, Arch. Neurol. & Psychiat. **34**:1286-1291 (Dec.) 1935.

Symonds [5] and many others, who recognized the frequent association of lesions and pathologic vessels but did not assign a causative role to the vascular change.

SUMMARY AND CONCLUSIONS

Sixty lesions from 5 cases of multiple sclerosis were studied by serial sections and their relation to the vascular system noted. The veins in the lesions were also compared with a group of 25 veins selected at random in the normal-appearing part of the brain in the same cases.

It was found that the lesions in the 5 cases studied were uniform so far as the number from each case would allow an opinion. When all 60 lesions were grouped together it was found that 20 were without a central vein, that 20 were oriented about a normal-appearing vein and that only 9 were about a vein in which a thrombus could be found. In 2 lesions the vein was collapsed, and in 9 it appeared distended. In 3 of the 9 lesions which had a thrombosed vessel the thrombus was completely outside the lesion; in 3 others the thrombus was partly inside and partly outside the lesion, and in only 3 could it be said that the thrombus coincided with the lesion. The occurrence of a thrombus in 1 of these was questionable, as the actual site of the thrombus was missing and its presence was inferred from the state of the vessel proximally and distally

No positive correlation was found between the lesions with a thrombus and the peculiarities of size or shape of the lesion, the degree of demyelination or the phagocytic cellular response. No positive correlation was found between the size or shape of the lesion and the presence or absence of a vein except that for some unexplained reason 4 out of the 5 irregular lesions were without central veins. When a vein was found within an ellipsoid or a cylindric lesion it was almost invariably oriented along the long axis of the lesion. There was a strong positive correlation between the perivascular cellular reaction of the central vein and the presence of a thrombus wholly or partly within the lesion.

The view that the demyelination in this disease is entirely unrelated to the vascular system does not seem tenable in the light of the foregoing observations. The view that the vascular changes, particularly thromboses, are an essential part of the pathogenesis of the lesion plaque seems equally untenable unless one accepts the assumption that venous thrombosis can disappear withrout trace, and at the same time exist long enough to cause permanent demyelination.

It is tentatively suggested that the thrombi observed are the result of the local absorption of thromboplastic substances released by the rapid breakdown of the myelin sheaths.

Dr. Ludo van Bogaert and Dr. H. J. Scherer, of the Institut Bunge, Antwerp, Belgium, furnished us with the clinical records and the pathologic reports, and Willetta Dow prepared the histologic sections.

HEMANGIOMA OF VERTEBRA ASSOCIATED WITH COMPRESSION OF THE CORD

RESPONSE TO RADIATION THERAPY

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The roentgenologic characteristics of hemangioma of the vertebral column were first described by Perman in 1926.[1] This report was based on the observations in a case of his own in which operation had been performed and also on a case previously reported by Gold[2]; in both compression of the cord was exhibited. The same roentgenologic features were reported by Bailey and Bucy[3] in 1929 in a case of compression myelopathy associated with a vertebral hemangioma. Since the publication of these reports vertebral hemangioma has been recognized clinically with increased frequency. The chief interest has centered in those cases in which the lesion caused or was associated with compression of the spinal cord or the cauda equina. These cases are relatively rare, 52 having been reported up to the present time[4]; the majority of vertebral hemangiomas are clinically silent.

In the 52 cases of compression of the cord and vertebral hemangioma reported in the literature the clinical picture was identical with the

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1. Perman, E.: On Hemangiomata in the Spinal Column, Acta chir. Scandinav. **61**:91-105, 1926-1927.

2. Gold, E.: Von den Wirbelveränderungen im Fälle eines Haemangioms an der Dura spinalis, Arch. f. klin. Chir. **139**:729-761, 1926.

3. Bailey, P., and Bucy, P. C.: Cavernous Hemangioma of the Vertebrae, J. A. M. A. **92**:1748-1751 (May 25) 1929.

4. (*a*) Schlezinger, N. S., and Ungar, H.: Hemangioma of the Vertebra with Compression Myelopathy, Am. J. Roentgenol. **42**:192-216, 1939. (*b*) Karshner, R. G.; Rand, W. C., and Reeves, D. L.: Epidural Hemangioma Associated with Hemangioma of the Vertebrae, Arch. Surg. **39**:942-951 (Dec.) 1939. (*c*) Rosentsweig, I. S.: Hemangioma of the Vertebral Column, Sovet. psikhonevrol. **14**:47, 1938. (*d*) Yuzhelevskiy, A. S.: Cavernous Hemangioma of the Vertebral Column with Symptoms of Transverse Myelitis, Vestnik khir. **52**:164-180, 1937. (*e*) de Luca, G.: Un caso di compressione da emangioma vertebrale, trattato con la radioterapia e clinicamente guarito, Arch. di radiol. **14**:271-278, 1938. (*f*) Freedman, E.: Hemangioma of the Vertebrae: Diagnosis and Treatment, Clin. Bull., Western Reserve Univ. **4**:34-36, 1940.

syndrome of any extradural tumor. Ever since it has been possible to recognize such cases clinically, the primary therapeutic procedure has been surgical. This has consisted of decompressive laminectomy; in some instances attempts were made to excise epidural hemangiomatous tissue if present. In many of those cases in which the patient survived the operation roentgen therapy was employed as a secondary measure. It is universally recognized that even the simplest operative procedure, namely, laminectomy, carries with it a high mortality, owing to severe and at times uncontrollable hemorrhage. This very fact led Nattras and Ramage to the employment of roentgen therapy as the primary and sole method of treatment.[5] Their patient demonstrated complete recovery from all symptoms of compression of the cord. Up to the present 11 additional cases in which this type of treatment was employed have been reported.[6] Good results were obtained in these cases, and in no instance has a fatal outcome been reported. We are presenting an additional case in which roentgen therapy was used as the sole therapeutic method, with an excellent clinical result.

REPORT OF A CASE

F. C., a 52 year old white man, a bus driver, entered the University Hospital on Oct. 3, 1939 complaining of "myelitis." In November 1938, eleven months prior to admission, he first experienced numbness, tingling and coldness in his feet and legs. These sensations slowly progressed upward to the costal margins. Five months after the onset of symptoms difficulty in walking was noticed, consisting of staggering gait and inability to maintain balance; at the same time stiffness and mild tenderness of the legs appeared. Walking became progressively worse until it could not be accomplished unaided. Urgency, frequency and occasional incontinence of urine, together with some disturbance of bowel function, was present for two months before admission. At no time during his illness did he have pain in his back, abdomen or legs. He had never sustained an injury to the back. The course of his illness was one of steady and slow progression, without remission at any time.

The family history was of no importance. It was learned that at about the age of 30 the patient had undergone an abdominal operation for what he reported as a "liver abscess."

Physical Examination.—The patient was well developed and well nourished, somewhat above the average in height and moderately obese. Many small heman-

5. Nattras, F. J., and Ramage, D.: Hemangioma of the Vertebra: A Cause of Cord Compression, J. Neurol. & Psychopath. **12**:251-257, 1932.

6. (*a*) Zawadowski and Grabarr: Un cas supposé d'angiome des corps et arcs vertébraux avec compression de la moelle, Rev. neurol. **1**:142-143, 1932. (*b*) Jarzymski and Zawadowski: Un cas d'angiome d'un corps vertebral, ibid. **1**:436-437, 1934. (*c*) Mossossian, Z.: Un cas d'hémangiome de la colonne vertebrale, J. de radiol. et d'électrol. **17**:363-371, 1933. (*d*) Michon, P.; Grégoire, and Lafont, J.: A propos du diagnostic de compression médullaire par hémangiome vertébral, Rev. neurol. **1**:565-571, 1935. Rosentsweig.[4e] de Luca.[4e] Freedman.[4f]

giomas were present in the skin, the greatest number being distributed over the back and abdomen in the region from the fifth to the tenth thoracic neural segment. There was no tenderness to percussion at any point over the spine. The rest of the physical examination gave negative results.

Neurologic Examination.—Examination of the cranial nerves revealed nothing abnormal except horizontal nystagmus, which was unsustained.

Marked loss of touch, pain and temperature sensations existed below the level of the eighth thoracic neural segment. In addition, an area of relative loss of these sensations was present on the right from the fourth to the eighth thoracic segment. Vibratory sensation was markedly impaired below the costal margin and was absent at the ankles. There was no recognition of the sense of position or motion in the toes. The ability to appreciate skin writing was impaired below the costal margin.

Motor examination of the lower extremities revealed marked spasticity, as well as pronounced weakness; these were more prominent on the right. The weakness was most pronounced in the distal portions; the patient was unable to move the toes and barely able to move the feet, but could move the legs and thighs to a moderate degree. Coordinative movements were executed poorly. On attempting to touch the knee with the opposite heel dysmetria and ataxia were evident. The gait was spastic and ataxic, and the patient was unable to walk without support. Station was poorly maintained, and the Romberg sign was positive. The strength and the muscle tone of the upper extremities were normal. In performing the finger to nose test a very mild intention tremor was seen.

The patellar and achilles reflexes were markedly hyperactive bilaterally; sustained patellar and ankle clonus was present. The biceps and triceps reflexes were found to be mildly hyperactive, and a positive Hoffmann sign was elicited on each side. An extensor (Babinski) response to plantar stimulation was obtained bilaterally. The Chaddock, Gordon, Oppenheim and Rossolimo signs were present bilaterally. The abdominal and cremasteric reflexes were absent.

Laboratory Data.—The Kahn reaction of the blood was negative; the red cell count was 5,370,000 per cubic millimeter, the white cell count 9,400 and the hemoglobin content 98 per cent (Sahli); the differential count of white blood cells was within normal limits; routine urinalysis showed nothing abnormal. Examination of the spinal fluid revealed an initial pressure of 170 mm. of water. A complete manometric block was found with jugular compression. The spinal fluid was clear but slightly xanthochromic; the Pandy reaction was strongly positive; both phases of the Nonne-Apelt test were positive; the Kahn reaction of the spinal fluid was negative; the gold colloidal and gum mastic curves were flat; the total protein was 190 mg. per hundred cubic centimeters, and the reaction for globulin was 4 plus.

Roentgenologic Examination.—Roentgenograms of the spine, taken on October 4, revealed the entire body of the seventh thoracic vertebra to have the characteristic appearance of hemangioma (fig. 1); this consisted of vertical striations of relatively increased bone density separated by vertical columns of decreased density. Suggestive, but inconclusive, evidence of involvement of the left pedicle was noted. The contour of the vertebral body was entirely normal.

Iodized poppyseed oil 40 per cent (descending type) was injected into the subarachnoid space in the lumbar region. On tilting the patient's head down the oil was seen to flow unimpeded until the level of the lower margin of the

seventh thoracic vertebra was reached, at which point a complete block was encountered and the advancing surface of the oil column assumed a concave shape, characteristic of the presence of an extradural lesion (fig. 2). After the injection of iodized oil into the cisterna magna with the patient in the erect position the oil descended to the level of the upper margin of the seventh thoracic vertebra, at which point an obstruction was encountered. This observation was made during the course of the fluoroscopic examination; roentgenograms, unfortunately, did not show this to good advantage, since some of the oil succeeded in passing posterior to the obstructing mass by the time the films were made.

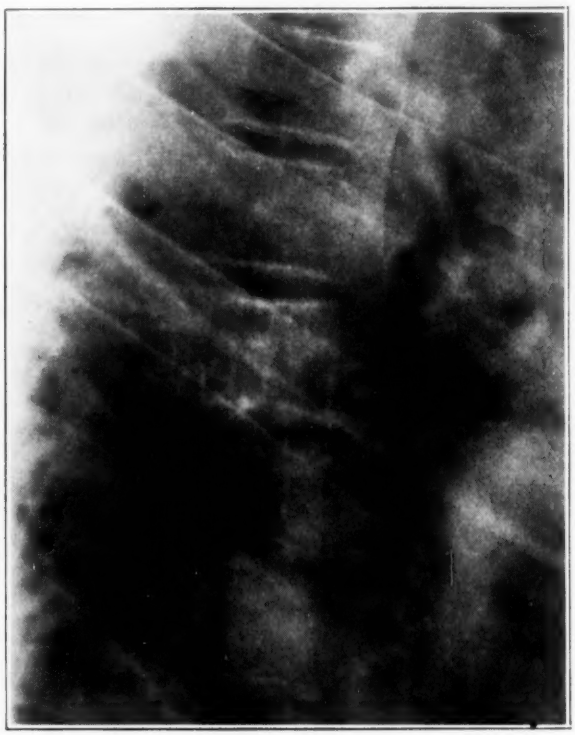

Fig. 1 (October 4).—Hemangioma of the seventh thoracic vertebral body, demonstrating the characteristic vertical striations. The size and shape of the involved body are normal.

These myelographic observations clearly demonstrated that a mass was present in the neural canal and extended from the lower to the upper border of the seventh thoracic vertebral body.

The history and clinical findings pointed to the presence of a tumor in the midthoracic region of the spinal cord. The myelographic examination disclosed the presence of a mass at the level of the seventh thoracic vertebral body. This body, as shown by the roentgenograms, was involved by a hemangioma. The intimate relation of the mass in the neural canal to the hemangiomatous vertebral

body led us to make the diagnosis of an epidural hemangioma associated with a hemangioma of the seventh thoracic vertebral body. The fact that multiple cutaneous hemangiomas were found, particularly in the area of the fifth to the tenth thoracic neural segment, may be considered as supportive evidence for this diagnosis.[7]

Because of the known danger of severe hemorrhage associated with surgical treatment of this condition the decision was made to use radiation therapy. Treatment was administered with the following physical factors: intensity, 200 kilovolts (175 kilovolts constant potential equivalent); filtration, 0.5 mm. of copper and 1.0 mm. of aluminum; half-value layer, 0.9 mm. of copper; skin target distance,

Fig. 2 (October 6).—Myelogram. Iodized poppyseed oil (descending type), introduced in the lumbar region, encountered an obstructing mass at the level of the lower margin of the hemangiomatous seventh thoracic vertebral body.

50 cm., and minute output, 50 r as measured in air. One field, measuring 13 by 15 cm., was centered over the seventh thoracic body. Treatment was administered daily from October 11 to October 24, using a daily dose of 200 r as measured in air, until a total dose of 2,400 r had been reached. A moderate cutaneous reaction developed, which regressed without incident, leaving slight residual pigmentation.

On the last day of treatment, October 24, the patient was reexamined. He had already noted slight increase in the strength of his lower extremities and reported

7. Cobb, S.: Hemangioma of the Spinal Cord Associated with Skin Naevi of the Same Metamore, Ann. Surg. **62**:641-649, 1915. Karshner, Rand and Reeves.[4b]

that he believed his gait was somewhat steadier. Neurologic examination revealed superficial sensation had returned to normal on the right side in the area of the fourth to the eighth thoracic neural segment. Objectively, the gait was noted to be a little steadier, and the strength of the legs was improved.

Two weeks after the last day of treatment, on November 8, the patient reported that the steadiness of his gait and the strength of his legs had continued to improve slowly but steadily. He also stated that all bowel and bladder disturbances had disappeared. Examination revealed that touch, pain and temperature were perceived with greater acuity than previously in the lower extremities, particularly on the left side. There was still definite hypesthesia below the eighth thoracic neural segment. For the first time vibratory sensation was perceptible at the ankles, although still considerably impaired. The senses of motion and position of the toes of the left foot showed improvement; however, these sensations were still considerably impaired on the right side. The lower extremities were less spastic than before, and their strength was increased, particularly on the left. The gait, though still spastic and ataxic, was steadier, and the patient was able to walk unaided. Clonus had been sustained prior to treatment; at this time it was unsustained. Plantar stimulation produced only flaring of the toes, but no dorsiflexion of the large toes. The deep tendon reflexes were still hyperactive.

Subsequent examinations, at intervals of approximately one month, revealed steady, continuous improvement. On June 11, 1940, eight months after the completion of treatment, examination revealed marked improvement in superficial sensory appreciation, though very mild hypesthesia persisted below the eighth thoracic neural segment. Vibratory sensation was only mildly impaired at the ankles, and the sense of motion and position of the toes was completely normal. The gait, though slightly ataxic, was good with the eyes either opened or closed. The strength of the lower extremities was good, and no spasticity was present. The heel to knee test was still performed with mild unsteadiness. The deep tendon reflexes remained hyperactive; the abdominal reflexes were present. Although typical flexion was not present on plantar stimulation, no true extensor response was elicited. No clonus could be obtained.

During the two months preceding June 11, 1940 virtually no improvement had taken place. It was thought advisable to administer more radiation therapy in the hope that further improvement could be obtained. With the same physical factors as those previously described, the patient was given daily 200 r as measured in air to one field, 13 by 15 cm., centered over the seventh thoracic vertebra until a total dose of 2,000 r had been administered. Treatment was begun on June 12 and completed on June 22. A moderately bright erythema developed, which regressed without incident. Two months later the field showed relatively marked pigmentation and slight residual dry scaling.

Examination two months after the second series of treatments disclosed sufficient further improvement to permit the patient to return to work. On Feb. 3, 1941, approximately sixteen months after his first series of treatments and eight months after the second series, the patient returned for a check-up examination. During the preceding six months he had been working steadily forty-eight hours a week as a motorman on a streetcar and was able to carry out his duties with full competence. Examination at this time revealed him to be normal in all respects except for a few patchy areas of minimal hypalgesia in the lower extremities and mildly hyperactive deep tendon reflexes. Roentgenographic examination of the spine revealed no obvious change in the appearance of the hemangiomatous seventh thoracic vertebral body.

COMMENT

Our patient demonstrated the findings described in the literature in proved cases of vertebral hemangioma associated with compression of the cord. Although no opportunity presented itself for observation of the gross or microscopic character of the lesion in the neural canal, sufficient evidence exists, nevertheless, to substantiate the diagnosis. The roentgenographic and myelographic evidence taken with the symptoms, physical signs and laboratory findings, in our opinion, amply justifies the diagnosis of an epidural hemangioma associated with a vertebral hemangioma of the seventh thoracic vertebra.

In general, present opinion favors surgical treatment as the primary method of therapy. Bailey and Bucy [3] stated that "the only treatment of any avail is laminectomy." This opinion appears to have been held by most writers on the subject.[8] The operation carries a high mortality rate because of the severe and at times uncontrollable hemorrhage which is invariably encountered. A review of the literature by Schlezinger and Ungar [4a] in 1939 revealed that operation had been performed in 23 cases. Karshner, Rand and Reeves [4b] reported 1 case, Yuzhelevskiy [4d] 3 cases and Freedman [4f] 1 case. In 6 of these 28 cases, that is in 21.4 per cent, the patient died after operation as the result of severe hemorrhage. In virtually every report the authors emphasize the difficulty and seriousness of the operation because of excessive bleeding. Of the patients surviving operation, 3 (10.7 per cent) were unimproved, 4 (14.3 per cent) showed improvement and 13 (46.4 per cent) recovered. The outcome in 2 cases is unknown.

Perman,[1] in 1926, employed radiation therapy as a postoperative measure. One third of all the patients treated by laminectomy have received some form of irradiation after operation. It is of interest that two thirds of these patients were classified by the various authors as showing complete recovery. The belief has been expressed by many that the scope of radiation therapy should be limited to that of a postoperative procedure [9]; Karshner, Rand and Reeves [4b] have gone so far as to state that "the use of roentgen therapy alone in cases of compression myelitis seems not only inadequate but hazardous."

There can be no disagreement that if one could substitute a procedure lacking the hazards of the surgical operation and yet capable of producing good therapeutic results a definite advance in the treatment of this disease would have been attained. We believe that radiation therapy as the primary form of treatment represents such a procedure. Substantiation for this statement is to be found in the fact that our patient showed an

8. Schlezinger and Ungar.[4a] Karshner and others.[4b] Perman.[1]

9. Bucy, P. C., and Capp, C. S.: Primary Hemangioma of Bone with Special Reference to Roentgenologic Diagnosis, Am. J. Roentgenol. **23**:1-33, 1930.

excellent clinical result after roentgen therapy and that reports of similar cases exist in the literature.

In 1930 Nattrass and Ramage [5] treated a patient with compression myelopathy associated with a hemangioma of the eighth thoracic vertebral body; slow and steady progression of signs and symptoms had been manifested from the onset, ten months before treatment. After roentgen therapy there was "immediate improvement which continued uninterruptedly" until complete recovery ensued.

Zawadowski and Grabarr,[6a] in 1932, reported a case of hemangioma of the third thoracic vertebral body with signs of compression in which the symptoms had been in existence for five months. After roentgen therapy the patient's ability to walk improved so markedly that he required no aid. In a later report (1934) Jarzymski and Zawadowski [6b] indicated that the improvement in this case continued until complete recovery had been attained. The report does not give the time which elapsed between completion of treatment and onset of improvement, but the impression is gained that improvement began relatively soon after treatment. In the second report a case of hemangioma of the ninth thoracic vertebral body with symptoms of three years' duration was described. In this case the patient demonstrated a marked compression syndrome with paralysis of the lower extremities and urinary retention. After radiation therapy improvement occurred to the extent that the patient was able to walk and the urinary retention disappeared, although recovery was not complete. The authors reported these observations three months after the time of admission to their clinic. Although exact information concerning the lapse of time between irradiation and onset of improvement is lacking, it is evident that the period must have been short.

Mossessian [6c] reported a case of multiple hemangiomas of the vertebral column with signs of compression of the cauda equina. According to the author, recovery followed the use of radiation therapy.

Michon, Grégoire and Lafont [6d] described a case of hemangioma of the fourth thoracic vertebral body in which the duration of illness was two and one-half years. Signs of marked compression of the cord were evident; the patient had complete paralysis of the lower extremities, anesthesia to the inferior mammary folds and bowel and bladder dysfunction. Roentgen therapy was begun on July 5 and completed on July 13. On July 13 evidence of returning function was present, consisting of active movements of the toes and the appreciation of sensation in several midthoracic neural segments. Improvement continued steadily, and four months later, except for ease of fatigue on walking and minimal residual signs of involvement of the pyramidal tract, the patient had recovered.

De Luca [4e] described a case of hemangioma of the eleventh thoracic vertebra with symptoms of progressive compression of the cord of one

and one-half years' duration. The patient had a complete transverse cord compression syndrome, with anesthesia below the eleventh thoracic neural segment, sphincteric disturbances and spastic paraplegia. Improvement was noted before the first series of roentgen treatments was completed; five months later the patient was well.

Rosentsweig [4c] reported 4 cases of this disease in which the sole treatment was roentgen therapy; in 3 of these cases complete recovery from signs of compression of the cord occurred, and in the other there was marked improvement. We were unable to ascertain the details of the case histories reported by this author.

Freedman [4f] reported the cases of 2 patients treated with roentgen irradiation only. In the first patient the twelfth thoracic vertebra was involved, with numbness, paresthesia from the knees down and complete paralysis of some of the muscle groups of the thighs, which made walking difficult even with crutches. Two and one-half years after irradiation the patient was well except for occasional pain in the legs. The second patient exhibited hemangioma of the fifth thoracic vertebra, with paraplegia, sensory and reflex changes and bladder dysfunction. Eighteen months after irradiation the patient was clinically well.

Thus, there are, including our own, 13 cases of vertebral hemangioma associated with compression of the cord in which radiation therapy was the sole method of treatment. (In the literature are to be found reports of a number of cases of vertebral hemangioma in which local pain in the back was the only symptom; in none of these was there any evidence of compression of the spinal cord or the cauda equina. In many of these cases treatment was by irradiation.[10] However, these cases are not pertinent to our discussion; we are concerned solely with instances of true compression of the cord, that is, the type of case in which general opinion has maintained that laminectomy is the treatment of choice.) In 10 of the 13 cases cited complete clinical recovery followed. Of the remaining 3, the patient in the case described by Michon, Grégoire and Lafont [6d] made an almost complete recovery, showing only ease of fatigue and minimal residual pyramidal tract signs; it is to be remembered that this patient had compression of the cord over a period of two and a half years and at the time of treatment had complete transverse myelopathy. In the case reported by Jarzymski and Zawadowski [6b] marked improvement occurred; at the time of reporting observations had been made for only three months. The course of events in other cases suggests

10. Ireland, J.: Hemangioma of the Vertebra, Am. J. Roentgenol. **28**:372-378, 1932. Lievre, J. A.: Les angiomes vertébraux, Presse méd. **42**:1571-1572, 1934. Barnard, L., and Van Nuys, R. G.: Primary Hemangioma of Spine, Ann. Surg. **97**:19-25, 1933. Scheel, A.: Vertebral Hemangiomas with Special Regard to Complications and Roentgenologic Diagnosis, Nord. med. (Norsk mag. f. lægevidensk.) **1**:854-862, 1939.

that this period is insufficient to demonstrate the maximum effect of the treatment. The third case was reported by Rosentsweig [4c] as one of marked improvement.

The literature contains only one report of an adverse effect following radiation therapy. Freedman [4f] has reported a case of hemangioma of the tenth thoracic vertebral body with progressive weakness of both legs and inability to walk in which complete paraplegia developed during the course of the roentgen therapy, necessitating laminectomy. The operation was performed in three stages because of difficulty in controlling bleeding. Two years after operation the patient was clinically well.

In contrast to the results obtained by radiation therapy, surgical statistics show that 1 out of every 5 patients subjected to operation died as the result of excessive hemorrhage. In nearly every case the postoperative course was stormy. Of the patients surviving operation, about 10 per cent showed no improvement. Therefore one third of the 27 patients subjected to laminectomy demonstrated an adverse result.

The primary argument against the use of radiation therapy for this disease is that delay in the release of the compression is inherent in the procedure. It is frequently stated that further damage to the spinal cord may result before the beneficial effects of irradiation develop. This contention is refuted by the experience in treating our patient. On the last day of a fourteen day period of treatment signs of beginning release of compression were demonstrable. An identical situation was encountered by Michon, Grégoire and Lafont.[6d] Nattras and Ramage reported immediate improvement following irradiation. As was pointed out previously, early improvement followed roentgen therapy in the case of Jarzymski and Zawadowski. De Luca found that regression of symptoms appeared before the first series of roentgen treatments was completed. Thus, in virtually every instance in which a detailed case history is available it is found that evidence indicating beginning release of compression appears immediately; the only exception is the case reported by Freedman.

It is an established fact that immediate decompressive laminectomy is imperative in instances of acute or sudden onset of marked compression of the spinal cord, since this may lead to necrosis of cord tissue because of obliteration of blood supply. The literature contains no case of vertebral hemangioma with compression of the cord in which such a condition was present. The nearest approach to this situation is in the case reported by Freedman, in which complete paraplegia developed during the course of radiation treatment. If this should occur, it is conceded that immediate laminectomy is the proper treatment.

It appears to us that ample evidence exists to justify our recommendation that radiation therapy should be the primary form of treat-

ment of this disease. Up to the present only 1 case of failure with radiation therapy has been reported. It is our suggestion that frequent thorough neurologic examinations should be performed during the first few weeks following adequate irradiation. In the event that no evidence of objective improvement has appeared at the end of a three or four week period laminectomy should be considered. It must be borne in mind that absence of response to adequate irradiation may be due to irreparable damage of the cord; in such a case laminectomy will be of no benefit.

SUMMARY

Fifty-two cases of vertebral hemangioma associated with compression of the cord are reported in the literature. Present opinion favors operation as the primary method of treatment; decompressive laminectomy has been performed on 28 patients. A case is reported in which roentgen therapy was employed as the sole means of treatment and in which an excellent clinical result was obtained. The literature contains 12 cases of patients treated in the same fashion, also with excellent results. In only 1 instance has an adverse effect been reported. Analysis of the available case histories reveals that there is no delay in the relief of compression with the use of radiation therapy. Surgical statistics show that 1 out of every 5 patients died as the result of excessive hemorrhage. Ample evidence exists to justify the recommendation that radiation therapy should be the primary form of treatment for this disease.

SUSCEPTIBILITY TO CONVULSIONS IN RELATION TO AGE

I. INFLUENCE OF ACID FUCHSIN ON RATS OF VARIOUS AGE GROUPS

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AND
I. ARTHUR MIRSKY, M.D.
CINCINNATI

The marked liability of young children and infants to convulsive disorders is well recognized.[1] A young child may react with convulsions to a stimulus, such as an infection or intoxication, which in an older subject would not produce this response. This peculiarity of the young child has led to much study and speculation, but as yet there is no adequate explanation of the responsible mechanism.

Although a wealth of clinical data has been accumulated with reference to this problem, a systematic investigation of the susceptibility of the organism to the development of convulsions in relation to age has not been made. Since the rat lends itself well to studies on convulsions,[2] this species was used to investigate the influence of various drugs and toxins on the development of convulsions at different age levels.

Certain acid dyes and viruses can penetrate into the nervous system of young animals, while they cannot do so in normal adult animals.[3] Thus, when trypan blue is administered parenterally the brain of the young animal (mouse; rabbit) stains vitally while that of the normal adult does not. These facts led us to investigate the influence of another acid dye, acid fuchsin, which does not penetrate the brain of adult mammals [4] but which, like other water-soluble, neurophilic, sulfonated

From the May Institute for Medical Research, the Jewish Hospital.

Aided by a grant from the Child Neurology Research (Friedsam Foundation).

1. Griffith, J. P. C., and Mitchell, A. G.: Textbook of Pediatrics, ed. 3, Philadelphia, W. B. Saunders Company, 1941.

2. Coombs, H. C.: Production of Experimental Convulsions in the White Rat, Am. J. Physiol. **101**:22-23, 1932. Sampson, W. L., and Fernandez, L.: Experimental Convulsions in the Rat, J. Pharmacol. & Exper. Therap. **65**:275-280, 1939.

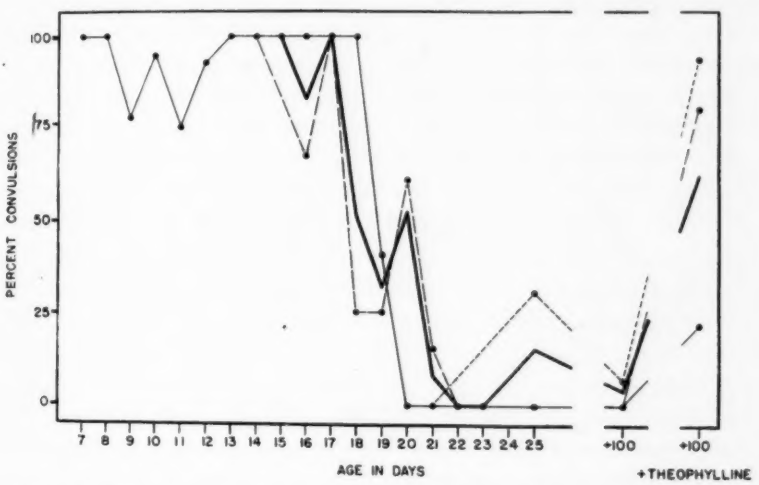
3. King, L. S.: The Hematoencephalic Barrier, Arch. Neurol. & Psychiat. **41**:51-72 (Jan.) 1939.

4. Wislocki, G. B., and King, L. S.: Permeability of the Hypophysis and Hypothalamus to Vital Dyes with Study of Hypophysial Vascular Supply, Am. J. Anat. **58**:421-472, 1936.

dyes, will produce strychnine-like convulsions in frogs.[5] The ability of this dye to penetrate the cells of the brain of young mammals has not been investigated, though some evidence exists that it can enter the cerebrospinal fluid of infants but not of adults.[6] It is known also that acid fuchsin does not produce convulsions in adult mammals.[5] Hence it became of interest to know whether or not this dye will act as a convulsant in young mammals, in which presumably it may be taken up by the nervous system.

METHOD

Groups of rats of both sexes which ranged in age from 7 to over 100 days were tested with varying doses of acid fuchsin. Each group consisted of from 10 to 40 rats. The youngest rats were 7 days of age, and a group of animals



Convulsant action of acid fuchsin on rats of different age groups. The various lines represent different doses of acid fuchsin: The light solid line indicates 0.5 mg. per gram of body weight; the line of long dashes, 1 mg. per gram; the line of short dashes, 2 mg. per gram, and the heavy line, the average of all doses.

The ordinate represents the percentage of animals of each group in which convulsions developed, and the abscissa the various age groups employed (see text).

was procured for every succeeding day of age up to 25 days. Rats over 100 days of age were considered as adults. In all, a total of 395 rats were used in the study (figure).

5. Barbour, H. G., and Abel, J. J.: Tetanic Convulsions in Frogs Produced by Acid Fuchsin and Their Relation to the Problem of Inhibition in the Central Nervous System, J. Pharmacol. & Exper. Therap. **2**:167-199, 1910-1911.

6. Pincherle, B., and Salom, G.: La barriera ematocefalica nel lattante. Pediatria **42**:239-265, 1934.

The acid fuchsin [7] was administered subcutaneously in a 2 to 5 per cent solution and in a dose of from 0.5 to 3.0 mg. per gram of body weight. No attempt was made to determine the minimal convulsant dose in any of the experimental groups.

RESULTS

Within forty-five minutes after the subcutaneous injection of the dye the animals began to show a generalized red color, and any urine passed thereafter was similarly stained. One to two hours after the administration of 0.5 mg. of acid fuchsin per gram of body weight to rats from 7 to 18 days of age the animals became restless. There followed muscular twitches, which produced jerky movements of one or another limb. Coordination of voluntary movements became impaired within the next hour, and this appeared to be associated with some muscular weakness, as indicated by wriggling movements and increasing inability to stand. Generalized convulsions of a tonic type developed within four hours after the injection of the dye; the hindlegs were extended away from the body, the forelimbs were extended under the body, the head was flexed on the chest and the abdominal muscles were contracted. The tonic convulsions frequently were associated with convulsions of a more clonic type; that is, clonic convulsions occurred at intervals, while the tonic convulsions persisted. The convulsions lasted several hours and terminated in death in 62 per cent of the animals under 19 days of age. This sequence of symptoms occurred in all the young rats in which convulsions developed, but the duration of convulsions varied from animal to animal.

The data are summarized in the figure, in which the susceptibility to the development of convulsions is expressed as the percentage of the total number of animals that were tested at any particular age and with any specific dose. Up to the age of 12 days, only 0.5 mg. of acid fuchsin per gram of body weight was administered. After that age a dose of 1.0 mg. was employed. Thus it may be noted that up to and including the age of 17 days 75 to 100 per cent of animals responded to the smaller dose of acid fuchsin with convulsions. In other experiments it was noted that even 0.25 mg. per gram of body weight was effective in producing convulsions in very young animals. Obviously, larger doses (e. g., 1.0 mg.) would likewise have produced convulsions, and hence such doses were employed only sporadically for animals between 12 and 17 days of age. On the eighteenth day of life the incidence of convulsions following the administration of 1.0 mg. of the dye dropped precipitously and continued to do so until the twenty-second day, when no

7. The acid fuchsin was purchased from the Coleman & Bell Company, Norwood, Ohio. This product is believed to be approximately four times as active as a German product sold before 1914.

convulsions occurred in a group of 18 rats. After that age neither 0.5 nor 1.0 mg. of acid fuchsin per gram of body weight produced convulsions. The dose was therefore raised to 2.0 mg., and this amount produced convulsions in 30 per cent of the 25 day old animals and in only 7 per cent of 44 adult animals.

In a previous communication, one of us (A. F.) [8] demonstrated that the preliminary treatment of frogs with theophylline will result in a decrease in the latent period necessary for the onset of convulsions consequent to the administration of acid fuchsin. Other studies indicated that the treatment of guinea pigs with theophylline permitted the penetration of ferrocyanide into the brain, a phenomenon which did not occur in the untreated pig.[9] Therefore the influence of theophylline on the effect of a subsequent injection of acid fuchsin was studied in the adult rat.

Adult rats were given two subcutaneous injections of from 0.12 to 0.24 mg. of theophylline with sodium acetate per gram of body weight (as a 4 per cent solution) in four hours, and one hour after the last injection various doses of acid fuchsin were administered. As illustrated in the figure, it is obvious that the adult rats thus treated became relatively susceptible to the convulsive action of acid fuchsin.

When the acid fuschin was administered to theophylline-treated adult rats by the intraperitoneal instead of the subcutaneous route the effects were still more marked. Doses as low as 0.25 mg. per gram of body weight were effective in producing convulsions in the theophyllinized adult rats in from forty-five to one hundred and twenty minutes, while doses as high as 2 mg. per gram did not produce convulsions in the nontheophyllinized rats receiving the dye by the same route.

The type of convulsions produced in the theophylline-treated adult rats differed from those in the young rats. In the latter the convulsions were predominantly tonic in nature with superimposed clonic convulsions and lasted many hours. On the other hand, the convulsions of the older rats were characterized by their clonic nature and short duration. Before the development of convulsions, the older rats became restless and salivated profusely, the reflex responses were augmented, the respiration became rapid, and apparent orthopnea occurred. In some instances the convulsions of the adult theophyllinized rat became so violent as to throw the animal to the top of its cage. Occasionally a convulsive seizure could be induced merely by blowing on the fur.

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8. Fröhlich, A., and Zak, E.: Theophyllin und seine Gewebswirkung als Mittel zur Potenzierung von Giften und Arzneien, Arch. f. exper. Path. u. Pharmakol. **121**:108-130, 1927; Der Ablauf von Vergiftungen an mit Theophyllin vorbehandelten Tieren, ibid. **143**:310-320, 1929; Die Kreislaufswirkung des Germanins, ibid. **185**:267-276, 1937.

9. Fröhlich, A., and Zak, E.: Unpublished data.

Since no attempt was made to determine the minimal convulsive dose in the various experiments in this study, relatively large doses probably were employed throughout the study. This may account for the high mortality that occurred. Adult animals frequently died about twenty-four hours after receiving from 2 to 3 mg. of acid fuchsin per gram of body weight, even though convulsions did not develop.

The intracerebral injection of from 0.1 to 0.5 mg. of acid fuchsin (in 0.25 cc. of an isotonic solution of sodium chloride) per animal weighing 200 to 300 Gm. resulted in violent convulsions. Four of 6 animals died soon after the development of convulsions. Profuse salivation and stimulation of the respiratory movements preceded the outbreak of convulsions, and death occurred with respiratory failure. The intracerebral injection of physiologic solution of sodium chloride in amounts similar to that used in the experiment just described produced no convulsions or other sequelae.

Several attempts to inhibit the convulsions of the very young rats consequent to the administration of acid fuchsin proved fruitless. Desoxycorticosterone,[9a] which may decrease capillary permeability,[10] was ineffective in preventing the development of the convulsions of very young rats treated with acid fuchsin.

COMMENT

Not only do young children show a greater susceptibility to convulsions, but their response to various pharmacologic agents is known to differ from that of adults. For example, infants are known to be very susceptible to the toxic effects of morphine and may have convulsions after its administration. However, few systematic studies have been performed with children or animals on the relation of age to susceptibility to the effects of drugs and toxins. Clark,[11] Obata [12] and Schlossmann [13] studied the relation between age and the responsiveness of rats and rabbits to atropine. These studies revealed that the younger the animal the greater is its susceptibility to the toxic effects of atropine and the development of tonic convulsions. Similarly, the toxicity of morphine in various age groups has been studied by Schlossmann,[13]

9a. Dr. E. Schwenk, of the Schering Corporation, supplied the desoxycorticosterone.

10. Menkin, V.: Effect of Adrenal Cortex Extract on Capillary Permeability, Am. J. Physiol. **129**:691-697, 1940.

11. Clark, A. J.: The Destruction of Alkaloids by the Body Tissues, Quart. J. Exper. Physiol. **5**:385-397, 1912.

12. Obata, T.: Ueber die Beziehung der Toleranz der weissen Ratten gegen verschiedene Arzneimittel zu ihrem Lebensalter, Jap. J. Med. Sc., IV, Pharmacol. **5**:83*-84,* 1931.

13. Schlossmann, H. A.: Influence of Age and the Action of Atropine and Morphine, J. Pharmacol. & Exper. Therap. **60**:14-31, 1937.

Döbeli [14] and Eddy,[15] who found that the minimal lethal dose of morphine was increased with age in rabbits. Likewise, the minimal convulsive dose increased with the age of the animal, the greatest change occurring soon after weaning (5 weeks of age).

The results of the present study with acid fuchsin are in accord with the observations of these authors in that they indicate a greater susceptibility of very young rats to the convulsive action of the dye. However, the striking phenomenon of a relatively sudden cessation in the response of rats to the convulsant action of acid fuchsin suggests that the responsible mechanism is different from that involved in morphine or atropine poisoning, since the latter drugs are still effective in adult animals while the dye is not. This, together with the observation by Pincherle and Salom [6] that the parenteral administration of acid fuchsin results in its appearance in the cerebrospinal fluid of infants during the first year of life and not thereafter, suggests some special mechanism which may be associated with the passage of the dye into the central nervous system. As was noted at the outset, acid fuchsin belongs to the class of dyes which do not stain the nerve cells of the brain of the adult animal but do stain those of the young animal. Hence, it may be assumed that since convulsions are produced in the young animal and not in the adult, some mechanism related to the passage of the dye into the brain tissue is associated with the susceptibility to convulsions.

The fact that theophylline, which makes possible the penetration of ferrocyanide into the brain of the guinea pig, also permits the development of convulsions in the adult rat in response to acid fuchsin is in accord with the hypothesis that one is dealing with the passage of the dye from the blood stream into the central nervous system. This leads to the discussion of the significance of the penetration of acid dyes into the brain.

Some investigators attribute the inability of acid dyes to stain vitally the cells of the central nervous system of the adult animal to the development of a functional or morphologic "hematoencephalic barrier." By this term is implied the existence of a block to the passage of the dye from the blood stream into the nerve cells. On the other hand, some believe that the nerve cells of the young animal have a special "affinity" for certain dyes of a particular electrical charge and that the permeability of a membrane is not involved in the phenomenon.[8] According to the latter hypothesis, this affinity is lost with age, presumably because of some change in the chemical constitution of the nerve tissue.

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14. Döbeli, E.: Ueber die Empfindlichkeit verscieden alter Tiere gegen die Opiumalkaloide, Monatschr. f. Kinderh. **9**:397-420, 1910.

15. Eddy, N. B.: Variations with Age in the Toxic Effects of Morphine, Codeine and Some of Their Derivatives, J. Pharmacol. & Exper. Therap. **66**: 182-201, 1939.

Not only does age influence the "barrier" or the "affinity," but inflammatory reactions in the adult brain result in restitution of the ability of acid dyes to enter the nerve cells. That is, damage to the brain results in some change which makes it respond like the very young brain. Morphologic and chemical studies reveal that with aging from birth to adult life there is an increase in the vascularity of the brain, alterations in the lipid and the water content, a decrease in the rate of lipid turnover and other changes which may or may not be responsible for the phenomenon under discussion.

The studies with theophylline suggest that a "barrier" may be the mechanism responsible for the inhibition of the vital staining of the adult brain, since it has been shown that theophylline increases the permeability of isolated blood vessels [16] and increases the ability of many tissues to take up various dyes.[17] Of course it is possible that theophylline may act by changing the chemical characteristics of the brain cells in such a manner as to increase their "affinity" for acid dyes, but as yet evidence for such a concept is lacking. Moreover, Aird's [18] studies with brilliant vital red led him to conclude that "the endothelium concerned with the formation of cerebrospinal fluid forms an effective protective barrier to the central nervous system." He attributed the fact that brilliant vital red will prevent cocaine hydrochloride convulsions to a decrease in the permeability of this "barrier."

Irrespective of whether one is dealing with a definite morphologic or functional "barrier" or with some chemical characteristic of the nerve tissue, the fact remains that this phenomenon is present in adult rats and absent in very young rats. Presumably this makes possible the action of a convulsant dye like acid fuchsin in young animals and not in normal adult animals. The aforementioned peculiar response of the young nervous system occurs not only with acid dyes but also with the parenteral administration of viruses. Thus, herpes virus [19] and equine encephalomyelitis virus [20] produce reactions in the brains of young animals and not in those of adults. Likewise, it is a well known

16. Zettler, L.: Die Wirkung von Gefassmitteln auf die Permeabilität der Arterien, Arch. f. exper. Path. u. Pharmakol. **185**:141-152, 1937.

17. Fröhlich, A.: Einfluss des Theophyllins auf die Durchlassigkeit der Gewebe mariner Tiere, Arch. f. exper. Path. u. Pharmakol. **166**:85-94, 1932. Fröhlich and Zak.[8]

18. Aird, R. B.: Mode of Action of Brilliant Vital Red in Epilepsy, Arch. Neurol. & Psychiat. **42**:700-723 (Oct.) 1939.

19. Andervont, H. B.: Activity of Herpetic Virus in Mice, J. Infect. Dis. **44**:383-393, 1929.

20. Sabin, A. B., and Olitsky, P. K.: Variations in Pathways by Which Equine Encephalomyelitic Viruses Invade the Central Nervous System of Mice and Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **38**:595-597, 1938.

phenomenon that the brains of young children dying with jaundice may be icteric while those of even severely jaundiced adults are colorless.

The fact that a dye like brilliant vital red prevents the convulsions of mice treated with various convulsants [21] does not contradict our observations. The studies with brilliant vital red were performed with apparently adult mice, and, as was demonstrated by Aird,[18] the dye did not penetrate the cortical cells. It is quite possible that the administration of the same dye to very young animals may produce convulsions even though the reverse occurs in adults. This aspect is now under investigation.

It may be postulated that a variety of organic substances can enter the cells of the central nervous system of the young animal much more readily than those of the normal adult. If this is the case, the increased liability of young children to convulsions may be directly related to the aforementioned phenomenon and the fact that infections produce convulsions may be attributable to the production of toxic products and their passage into the brain.

SUMMARY

Groups of rats from 7 to over 100 days of age were subjected to the subcutaneous administration of acid fuchsin in doses of 0.5 to 1 mg. of body weight per gram. This resulted in tonic and clonic convulsions in 75 to 100 per cent of animals at every age level below that of 17 days. On the eighteenth, nineteenth and twentieth days of life the incidence of convulsions fell off rapidly, until the twenty-first day, when the incidence was negligible. Increasing the dose of acid fuchsin after that age produced insignificant change in the incidence of convulsions.

Adult rats did not have convulsions even when acid fuchsin in doses as high as 3 mg. per gram of body weight was administered by either the intraperitoneal or the subcutaneous route.

The administration of theophylline to adult rats resulted in a change in their response to acid fuchsin, so that the intraperitoneal injection of doses as low as 0.25 mg. of the dye per gram of body weight produced convulsions.

The relation between the development of convulsions and the passage of the dye into the central nervous system is discussed (hematoencephalic barrier). It is emphasized that the ability of the dye to enter the central nervous system decreases with age and that its ability to produce convulsions varies accordingly.

The possibility that the increased liability of infants to convulsions may be due to the passage of toxic substances into the central nervous system is discussed.

21. Cobb, S.; Cohen, M. E., and Ney, J.: Brilliant Vital Red as an Anticonvulsant, J. Nerv. & Ment. Dis. **85**:438-441, 1937; Anticonvulsant Action of Vital Dyes, Arch. Neurol. & Psychiat. **40**:1156-1177 (Dec.) 1938. Aird.[18]

BIOCHEMICAL DISTURBANCES IN MENTAL DISORDERS

I. ANTI-INSULIN EFFECT OF BLOOD IN CASES OF SCHIZOPHRENIA

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AND
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This paper is a report of the first phase of a research problem based on the assumption that in the insulin and the convulsive treatment of schizophrenia there are certain trends in the mode of action which are common to both and have been defined clearly enough to form a basis for further investigations.

The experiments here reported were undertaken to test the assumption that one of the accompaniments, and possibly a basic factor, of schizophrenia may be a disturbance of the carbohydrate metabolism acting antagonistically, in a measure, to the normal carbohydrate metabolism.

REPORT OF INVESTIGATION

The first part of this work was done in cooperation with Dr. B. Rohny, of Budapest, Hungary. Three methods were followed in investigating the diabetogenic action of the anterior lobe of the hypophysis.

1. The effect of Hoffman's "carbohydrate metabolism hormone" was determined. The method is as follows: The patient is first given 120 Gm. of dextrose by mouth after fasting. Two hours later blood is drawn from the vein and centrifuged after coagulation. Of the serum thus obtained 3 cc. is injected subcutaneously into rats, and the liver glycogen of the experimental animal is then determined at the end of two hours. Under these conditions the carbohydrate metabolism hormone reduces the glycogen content of the liver.

The blood of 10 normal persons and of 10 schizophrenic patients was used for these investigations. It was found that the average

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This work was aided by a grant from the committee on scientific research of the American Medical Association and by Mr. Oscar Mayer, of Chicago.

reduction of the liver glycogen caused by the blood serum of the schizophrenic patients was just as great as that produced by the serum of the normal healthy subjects. It can be concluded, therefore, that there was no change in the carbohydrate metabolism hormone of the blood serum of schizophrenic patients.

2. The second method utilizes the observation that there is a characteristic hypophysial deficiency associated with starvation hypoglycemia. The daily blood sugar level was determined for 44 schizophrenic patients during a five day fast. It was found that frequently the blood sugar level of the patients dropped by the third or fourth day to 60 mg. per hundred cubic centimeters and then gradually rose. In general, this reaction followed the same course as that which occurs in the case of the fasting normal subjects.

3. The test of Tannhauser and Pfitzer was made. This consists of giving an intravenous infusion of 500 cc. of a 7 per cent solution of dextrose and recording the blood sugar value at various intervals. In normal subjects the blood sugar returns to its original level fifteen minutes after the infusion is given. But if there is a hepatic deficiency the blood sugar level will remain above normal for a much longer time. It is easy to see that the same result will be produced (1) if the patient has a deficiency of insulin production or (2) if some pathologic endocrine factor prohibits or hinders the effect of the normally produced insulin.

All of the 20 schizophrenic patients tested showed a delay in the return of the blood sugar to a normal level after the infusion. In 2 patients the blood sugar returned to the original level after thirty minutes (fifteen minutes is the normal time); in 3 after forty-five minutes; in 4 after sixty minutes; in 3 after seventy-five minutes; in 5 after ninety minutes, and in 3 after one hundred and twenty minutes.

It can be concluded, therefore, that in these 20 untreated schizophrenic patients there was some disturbance of the carbohydrate metabolism characterized by a delayed utilization of blood sugar. The delayed utilization of dextrose given intravenously may be due to one of two factors: (1) a low insulin level of the blood of schizophrenic patients or slow mobilization of the insulin actually needed, or (2) the overactivity of some product of endocrine origin which inhibits or hinders the effect of insulin normally produced.

Several considerations favor the second possibility and oppose the first. If the insulin level of the blood of schizophrenic patients were low one would expect a high level of sugar in the blood, or at least a tendency toward it. In fact, however, the blood sugar level of schizophrenic patients tends to low normal standards. Also, the coincidence

of diabetes and schizophrenia in the same person is rather rare. Therefore, the second possibility, the presence of a substance in the blood of schizophrenic patients which actually inhibits or hinders the effect of normally produced insulin, must be evaluated. This substance must be of anti-insulin nature.

In the previously cited experiment (the Tannhauser and Pfitzer test) the quantitative relation of such a substance to 35 Gm. of dextrose is measured by the prolongation of the period of hyperglycemia. This time is fifteen minutes for normal persons; for schizophrenic subjects it increases twofold to eightfold.

The next step was to determine the presence of this substance in blood obtained from schizophrenic patients and to demonstrate its presence by the effect of the blood of such patients on the action of insulin when injected into test animals.

To obtain standards for comparison, 20 rabbits were given injections of the blood of normal persons and later received a certain dose of insulin. Each rabbit weighed 2,000 Gm. and was used only once for these experiments. Each animal was made to fast for twenty hours before the experiment and was kept in the laboratory at an even temperature. Each animal received intraperitoneally 20 cc. of fresh whole blood taken from students and nurses who had also been fasting for twenty hours. One hour later the blood sugar of the animals was determined by the method of Hagedorn and Jensen. Immediately after the first determination of blood sugar each animal received 1 international unit of insulin subcutaneously. At the end of thirty minutes the blood sugar was again determined and each hour thereafter until the fifth hour.

The comprehensive curve of these 20 experiments is given in figure 1.

As the curve shows distinctly, normal blood given one hour before the insulin does not protect the animal against the effect of the insulin. The average blood sugar curve is a typical one for insulin hypoglycemia. Further analysis of the individual curves yields the following data: Eight animals (40 per cent) had hypoglycemic coma between the first and the third hour after injection. One animal recovered spontaneously from the coma; 7 animals (35 per cent) died in coma. In 5 animals (25 per cent) the loss of blood sugar was less than 60 per cent in the third hour (the actual values were 50, 53, 55, 55 and 57 per cent). We may assume that in these 5 instances the normal blood protected the animal to some extent against the action of insulin.

In a second series of experiments, samples of blood from 7 epileptic patients were given to 7 animals under the same experimental conditions; that is, both the experimental animals and the patients fasted for twenty hours before the blood was taken. Three of the 7 animals

died in hypoglycemic coma in the third or fourth hour after the injection of insulin. Death occurred at the point at which the loss of blood sugar surpassed 75 per cent.

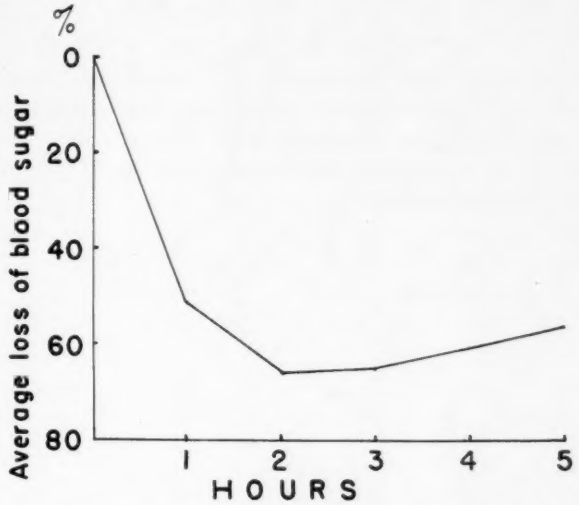

Fig. 1.—Average loss of blood sugar for animals treated with 20 cc. of normal blood and 1 unit of insulin. Each point corresponds to the average value for 20 experiments.

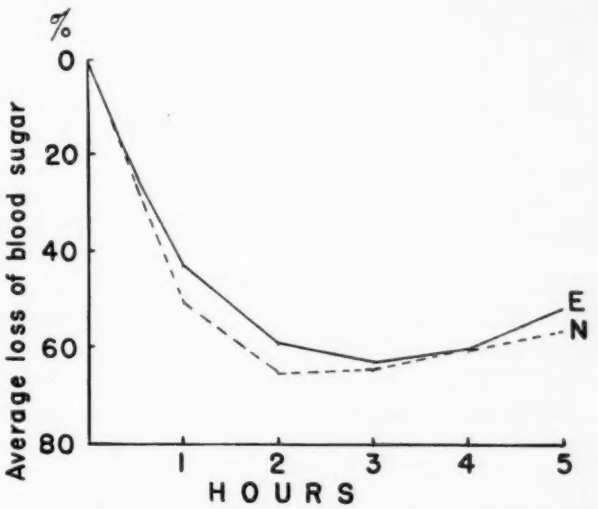

Fig. 2.—*E* is the average curve for loss of blood sugar for animals given 20 cc. of the blood of epileptic patients and 1 unit of insulin, and *N*, the control curve, as shown in figure 1.

The average curve for these experiments is shown in figure 2. As can be seen, the curve for the animals receiving blood from epileptic

patients and the curve for those receiving blood from normal subjects are closely parallel at the first determination, made thirty minutes after the injection of insulin. After that point the two curves diverge, but the difference between them is nowhere greater than 7 per cent. This, we believe, cannot be considered significant.

In a third series of experiments, the blood of schizophrenic patients was given to experimental animals under the same conditions (20 cc. of blood of patients who had fasted for twenty hours before blood was taken plus 1 unit of insulin). The mean blood sugar curve for this series of 51 experiments was distinctly different from the preceding curves, as can be seen in figure 3.

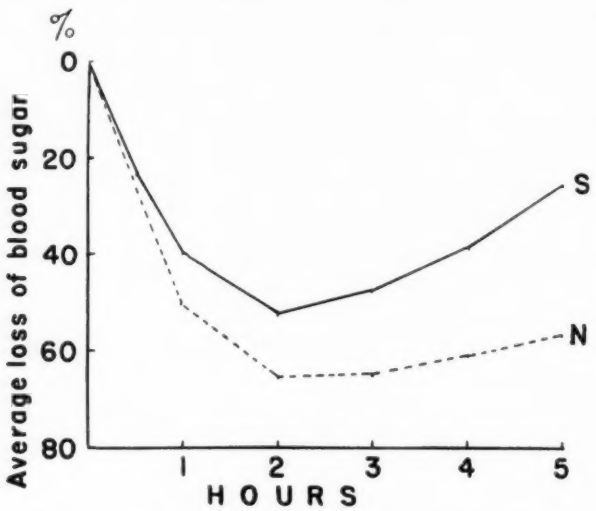

Fig. 3.—*S* is the average curve for the loss of blood sugar for 51 animals given the blood of schizophrenic patients, and *N*, that for 20 animals given the blood of normal subjects.

The results of the experiments are given in the accompanying tables. Table 1 shows the experimental data obtained by injection of normal blood plus insulin; table 2 contains the data on the experiments with blood from schizophrenic subjects. The degree of hypoglycemia is expressed in percental losses of the initial blood sugar. Incidentally, the means of the blood sugar values for the two groups of rabbits at the beginning of the experiments were practically identical (96.0 per cent for the group receiving blood from normal subjects and 97.8 per cent for the group receiving blood from schizophrenic patients).

The statistical evaluation gives difficulties in each series, for a number of the animals died of hypoglycemic shock during the experiments. If we had omitted these data for the animals which died, we

should have implied that the blood sugar values for these animals corresponded to the mathematical average for the surviving animals, and so our figures would have been misleading. Consequently, we corrected our totals by adding the last determined blood sugar value of each of the animals which died. For example, in the case of animal 15 (table 1) the decrease in the blood sugar thirty minutes after the injection was 28 per cent of the initial value; thirty minutes later it was 63 per cent; then the animal died before a third determination of the blood sugar could be made. Accordingly, the blood sugar values for that animal are given in each succeeding column as a 63 per cent loss.

TABLE 1.—*Hypoglycemic Changes Expressed in Percentages of the Initial Values After Injection of Normal Blood and Insulin*

No. of Animals	Time After Injection					
	30 Min.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.
1	38	46	60	55	43	35
2	47	56	62	65	43	40
3	52	67	78	Died		
4	17	58	63	73	Died	
5	29	51	75	64	57	52
6	23	43	76	69	59	47
7	5	38	64	61	51	42
8	19	59	69	69	75	68
9	14	48	65	62	58	53
10	39	50	66	63	63	58
11	22	41	52	57	53	37
12	29	52	66	72	66	64
13	26	44	64	55	49	45
14	11	40	58	50	43	37
15	28	63	Died			
16	29	50	66	53	53	50
17	25	49	75	Died		
18	17	57	72	Died		
19	30	50	60	70	Died	
20	19	39	61	72	Died	
Totals, omitting animals which died	519	1,011	1,252	1,010	1,713	628
Totals, corrected for animals which died	519	1,011	1,315	1,298	1,216	1,131
Means of corrected values	25.9	50.5	65.7	64.9	60.8	56.5

The data so obtained represent the corrected totals from which we calculated the corrected means. Statistical evaluation of the first hour values for both the group receiving blood from normal patients and that receiving blood from schizophrenic patients showed that the probable error of those values in the case of the group receiving normal blood is $\pm$ 1.29 per cent. Consequently, the average loss of blood sugar for this group at the first hour is 50.55 $\pm$ 1.29 per cent.

The probable error at the first hour for the group receiving blood from schizophrenic patients is $\pm$ 1.11 per cent, and the average loss of blood sugar at that time is 40.00 $\pm$ 1.11 per cent. The probable error of the difference of these two means is $\sqrt{1.29^2 + 1.11^2}$, or $\pm$ 1.70 per cent. Now the difference between the two means is 10.55

per cent, and therefore the critical ratio, 10.55 divided by 1.70, is 6.79. Any critical ratio of 4.00 or greater can be regarded as statistically significant.[1]

TABLE 2.—*Hypoglycemic Changes Expressed in Percentages of the Initial Values After Injection of Blood of Schizophrenic Patients and Insulin*

No. of Animals	Time After Injection					
	30 Min.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.
1	31	37	47	33	22	18
2	28	30	25	0	0	0
3	54	59	69	51	45	44
4	23	53	68	74	43	21
5	41	45	67	57	34	34
6	35	44	56	67	44	25
7	44	53	63	70	52	33
8	29	46	59	57	46	19
9	28	42	56	56	44	26
10	24	39	51	34	16	4
11	16	35	54	35	14	14
12	58	68	71	71	61	33
13	21	36	56	52	36	17
14	21	26	47	42	18	13
15	21	21	38	33	18	0
16	24	39	61	66	44	20
17	2	25	46	48	39	9
18	14	35	35	27	12	0
19	13	30	46	39	23	0
20	44	50	62	44	36	13
21	2	26	50	50	44	25
22	25	43	48	42	29	23
23	27	59	75	71	63	41
24	44	63	74	71	65	63
25	32	39	Died			
26	31	42	64	55	33	31
27	6	39	64	61	51	42
28	13	44	61	58	50	46
29	6	46	63	75	80	Died
30	39	56	64	59	48	45
31	10	33	45	38	24	22
32	14	47	55	45	32	29
33	33	56	54	38	24	15
34	18	44	56	46	32	27
35	24	35	45	30	29	12
36	8	21	17	8	1	0
37	36	58	70	Died		
38	11	29	56	42	30	18
39	14	43	43	37	26	19
40	24	41	43	37	27	18
41	24	43	62	57	48	39
42	6	25	51	56	46	32
43	8	16	9	1	1	1
44	21	45	59	69	73	Died
45	20	35	46	46	39	4
46	12	31	54	57	48	35
47	8	15	49	45	32	20
48	20	44	52	46	35	20
49	27	38	51	44	38	25
50	20	43	61	61	43	35
51	21	28	34	33	21	12
Totals, omitting animals which died	1,175	2,040	2,652	2,334	1,849	1,042
Totals, corrected for animals which died	1,175	2,040	2,691	2,443	1,958	1,304
Means of corrected values	23.0	40.0	52.8	47.9	38.4	25.6

This means that the differences between the mean of the values for the group receiving blood from normal subjects and that for the group

1. Pearl, R.: Introduction to Medical Biometry and Statistics, ed. 3, Philadelphia, W. B. Saunders Company, 1940.

receiving blood from schizophrenic patients at the first hour period are much greater than could have arisen by chance, and since the differences for succeeding hours become even greater, further statistical evaluation seems unnecessary. (The differences between the mean of the values for the group receiving blood from normal subjects and the mean for the group receiving blood from schizophrenic patients are: 10.55 per cent at the first hour, 12.90 per cent at the second hour, 17.0 per cent at the third hour, 22.4 per cent at the fourth hour and 30.9 per cent at the fifth hour.)

As a result of these experiments, we conclude that the blood of schizophrenic patients contains a factor which inhibits the effect of insulin. Analysis of the individual curves reveals that the amount of this inhibitory factor which is present in each schizophrenic patient's blood is not the same. The "average" curves for the animals given blood from schizophrenic patients and for animals given blood from normal subjects have two distinct features: the degree of loss of blood sugar and the rate of recovery.

It can be seen that the average curve for animals receiving blood from schizophrenic patients and the average curve for those receiving blood from normal subjects differ in these two respects: 1. The greatest loss of blood sugar indicated by the average curve for animals receiving blood from schizophrenic subjects is 52.8 per cent, and that indicated by the curve for animals receiving blood from normal subjects is 65.7 per cent. 2. The recovery of the curve for animals receiving blood from schizophrenic patients begins at the second hour and proceeds continuously at an increasing rate. The differences in the mean values for this group are as follows: between the second and the third hour, 4.9 per cent; between the third and the fourth hour, 9.5 per cent, and between the fourth and the fifth hour, 12.8 per cent. The recovery of the curve for animals receiving blood from normal subjects is sluggish; the difference between the second and the third hour is 0.8 per cent, between the third and the fourth hour 4.1 per cent and between the fourth and the fifth hour 4.3 per cent, so that in the fifth hour the average loss is still 56.5 per cent, as compared with the 25.6 per cent loss of blood sugar at the same time for the group receiving blood from schizophrenic patients.

As a result of the variations in the amount of the inhibitor factor in individual samples of blood from schizophrenic patients, the variations in the individual curves for animals receiving blood from schizophrenic patients are far greater than they are in the curves for animals receiving blood from normal subjects. Consequently, the average curve for the group receiving blood from schizophrenic patients does not express anything about schizophrenia itself except to indicate that schizophrenic patients generally have more anti-insulin factor in their

blood than do normal persons. In comparing individual curves for the two groups, one frequently observes that the lowest point of an individual curve for an animal receiving normal blood is even higher than the lowest point of the average curve for animals receiving blood from schizophrenic patients. There are, however, certain characteristic features which belong to curves for the latter group only. Figure 4 shows such a curve. On the ordinates the loss of blood sugar is expressed in percentages of the original values. The abscissas mark the time of the blood sugar determinations. For each point of time two columns of figures indicate the number of animals in each group (those receiving normal blood at the left and those receiving blood from schizophrenic patients at the right) showing the same decrease

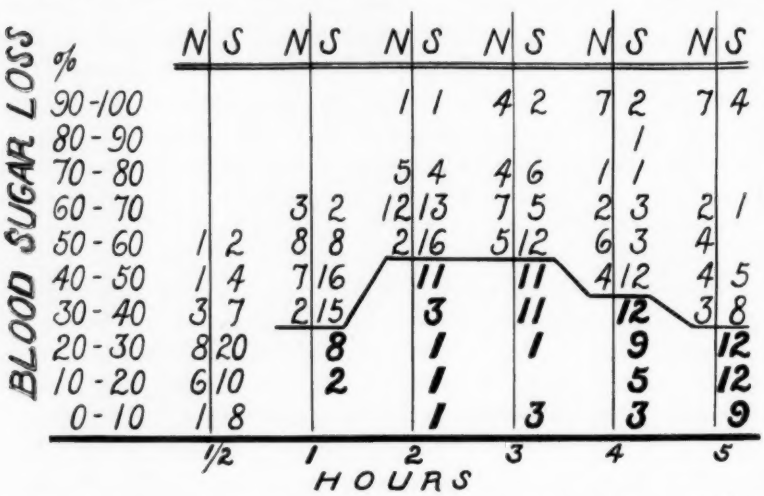

Fig. 4.—Values for loss of blood sugar at different periods after injection for animals treated with blood from normal subjects and for animals treated with blood from schizophrenic patients.

of blood sugar as that expressed on the ordinate at the left. It is seen that in the first thirty minutes there was no significant difference between the two groups of animals. But at the first hour each of the animals treated with normal blood plus insulin showed a loss of blood sugar of more than 30 per cent, as compared with the group treated with the blood of schizophrenic patients, in which there were 10 animals (19 per cent) which had a loss of blood sugar of less than 30 per cent. In the second hour of the experiment each of the animals treated with normal blood manifested a loss of blood sugar of more than 50 per cent. At the third hour about 50 per cent of the group receiving blood from schizophrenic patients lost less than 50 per cent and all of the group receiving normal blood showed a loss greater than this. Recovery

began at the fourth hour, but the animals treated with blood from schizophrenic patients were protected against the effect of insulin and consequently their rate of recovery was higher. This is evidenced by the fact that 29 animals (57 per cent) of this group exhibited a loss of blood sugar of less than 50 per cent and all the group treated with normal blood had a loss greater than this. In the fifth hour 33 animals (64.7 per cent) of the group receiving blood from schizophrenic patients had a loss of less than 30 per cent, while the values for all of the group receiving normal blood were above this level. This suggests a curve which on the basis of our experiment sharply differentiates schizophrenic patients from normal and epileptic subjects. Under the experimental conditions set forth, this curve would show a loss of blood

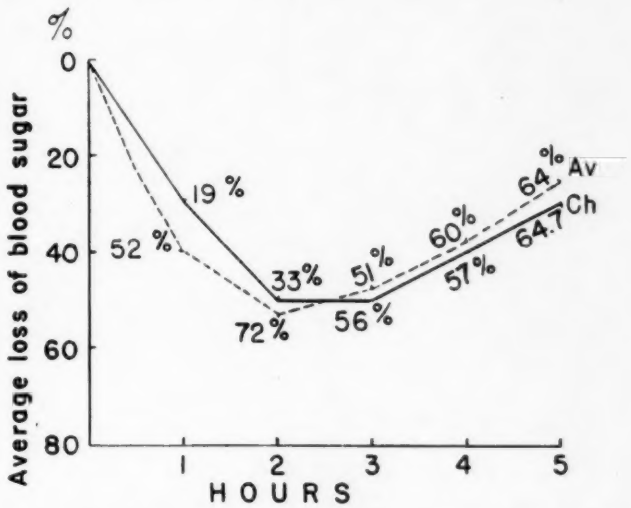

Fig. 5.—*Av* shows the average schizophrenic curve, and *Ch*, the "characteristic" schizophrenic curve.

sugar of 30 per cent or less in the first hour, of 50 per cent or less in the second hour, of 50 per cent or less in the third hour, of 40 per cent or less in the fourth hour and of 30 per cent or less in the fifth hour.

We believe that this blood sugar curve for the experimental animal is characteristic of schizophrenia; hence we shall call it the "characteristic schizophrenic curve."

The differences between the "average" and the "characteristic" schizophrenic blood sugar curve are shown in figure 5. While the difference is negligible after the third hour, it is rather noticeable between the first and the third hour. This can be seen from the percentile numbers of the experimental animals which manifest the same average loss of blood sugar at a given time. Nineteen per cent of

the animals manifest the "characteristic" and 52 per cent the "average" schizophrenic curve at the first hour; 33 per cent show the "characteristic" and 72 per cent the "average" schizophrenic curve at the second hour. From the third hour the two curves run parallel; the differences are insignificant, and the number of animals which manifest the "characteristic" and those which manifest the "average" schizophrenic curves are practically the same.

Several cross experiments were carried out in order to make sure that the demonstrated differences indicate a reaction to the blood of schizophrenic subjects, and not an individual reaction on the part of the animal. The result of 1 of these experiments is to be seen in

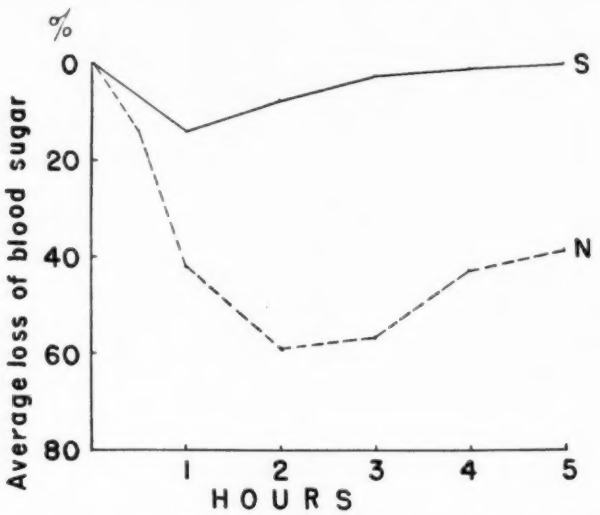

Fig. 6.—*S* is the curve for loss of blood sugar after injection of blood from a schizophrenic patient plus insulin, and *N*, the curve after injection of normal blood plus insulin, both in the same animal.

figure 6. In this case the same animal was tested twice. First, it received 20 cc. of blood from a schizophrenic patient and then, as usual, 1 unit of insulin. The blood sugar values are shown in curve *S*. Ten days later the same animal received 20 cc. of blood from a normal subject and the usual 1 unit of insulin. The resulting blood sugar values are shown in curve *N*. Altogether, we made 9 such cross experiments, and in all of them we found that the animals reacted in the same way; i. e., the decrease of blood sugar was less when they were treated with blood from schizophrenic patients than it was when they were treated with blood from normal subjects. The differences varied from case to case, which is easily explained when it is understood that the disturbance present in the schizophrenic patients varies in

degree. In some cases, as in figure 6, the anti-insulinic factor of the blood of a schizophrenic patient was present in such a large amount that it almost abolished the effect of insulin; in other cases the inhibiting factor was not so accentuated. These experiments can be evaluated in a qualitative sense only, because even one injection of insulin alters the reaction of the animal to this substance, and it is not known whether or not the same phenomenon occurs with the anti-insulinic factor.

Of several interesting side lights which presented themselves in the course of this work, one is the activity of the anti-insulinic factor not only in the animal body but in the test tube as well. A number of experiments were done with blood of both normal and schizophrenic subjects treated in the following manner:

Ten or 15 cc. of blood serum was prepared under sterile precautions. One unit of insulin was added and the mixture incubated at 37 C. The mixture was then injected subcutaneously or intraperitoneally into the animals used for the experiment, and the blood sugar values were determined in the usual way. The resulting curves corresponded to those presented in this paper.

A short time before the results of these researches were presented we learned from Dr. S. H. Kraines, in the course of a discussion, that in 1938 he had made similar experiments, with results similar to those reported here. In his work he injected into rabbits 2 cc. of serum of schizophrenic patients and of normal persons with 0.5 unit of insulin per kilogram of body weight. Changes in the blood sugar were then determined. His results are shown in figure 7. His curves are practically identical in shape with those in figure 3 of this study. The quantitative difference between our curve and his is due to the fact that he used only 2 cc. of serum and we used 20 cc. of whole blood.

This and several similar experiments indicate to us that the differences in the blood sugar curves are due to the differences in the blood injected and not to the variable sensitivity of the animals to insulin.

After summing up our results, we were interested in learning whether blood from various types of schizophrenic patients would give significantly different results in this test. We selected from our material 5 patients for whom the diagnosis was schizophrenia with manic features or mania with schizophrenic features. The average blood sugar curve for animals receiving blood from these patients is shown in figure 8. In all cases the experimental animals died in hypoglycemic coma between the third and the fourth hour of the experiment. Their blood sugar curves were deep normal ones, thus proving that the schizophrenia-like diseases in question differ not only in their clinical pictures but also in their pathogenesis.

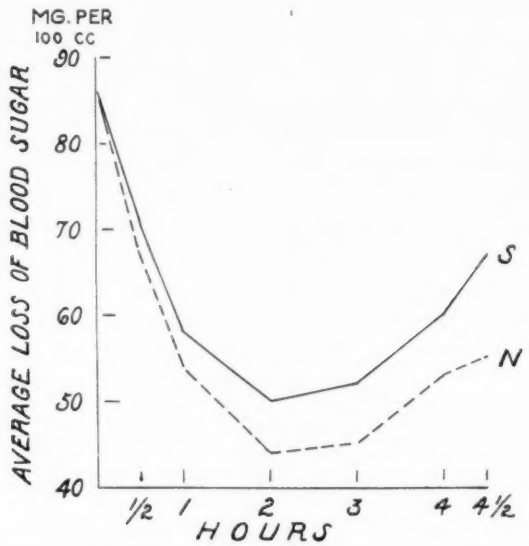

Fig. 7.—Values obtained by Dr. S. H. Kraines, showing loss of blood sugar after injection of 2 cc. of serum and 0.5 unit of insulin in each of several rabbits. *S* indicates curve after injection of blood from schizophrenic patients, and *N*, curve after injection of blood of normal subjects.

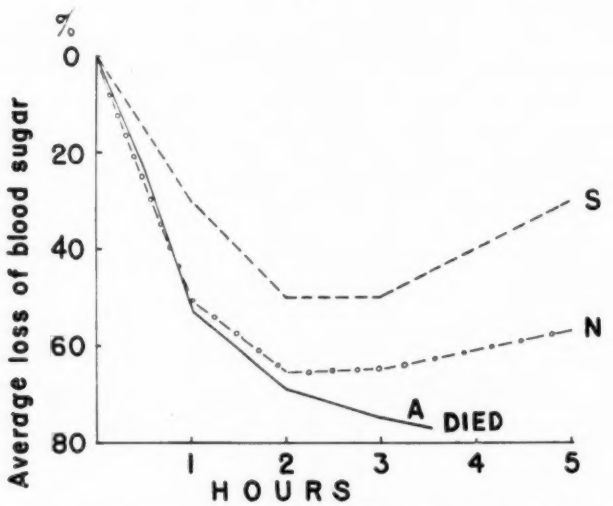

Fig. 8.—*S* is the curve for loss of blood sugar in animals given the blood of patients with typical schizophrenia plus insulin; *N*, that for animals given blood of normal subjects plus insulin, and *A*, that for animals given blood of patients with atypical schizophrenia plus insulin.

It is generally assumed that schizophrenia is a collective name for similar disease patterns of different origins. Many attempts have been made to subdivide or to group these different kinds of schizophrenia according to various criteria, most of which have to do with the supposed etiologic factors. Thus, schizophrenia has been assumed to exist in "organic," psychogenic, hereditary, acquired, endogenous and exogenous forms. Though the concepts could be stated with some appearance of validity, no one has been able to establish determining factors which would differentiate one form from another.

We believe that by means of the test here presented we are able to differentiate at least two forms of schizophrenia. The schizophrenic pattern as it appears in about 60 per cent of the cases is characterized by the presence of the anti-insulin factor studied. A similar clinical pattern, or syndrome, appearing in about 40 per cent of the cases seems not to be accompanied by the presence of an anti-insulinic factor and to be due to other possible disturbances.

Another important consideration of this work is illustrated in figure 5. This shows two curves, the average, or mean, curve of our investigations and the so-called characteristic schizophrenic curve. The mean curve expresses only the mathematical average of our curves and reveals that 52 to 72 per cent of the experimental animals manifested a curve within $\pm$ 5 per cent of the average. The characteristic schizophrenic curve was found only when experimental animals were given injections of blood from schizophrenic patients and insulin.

This implies that under our experimental conditions the blood sugar curve of the experimental animal can be used as a diagnostic test for schizophrenia accompanied by the presence of an anti-insulinic factor.

A positive reaction to the test is one in which the loss of blood sugar is not greater than 30 per cent in the first hour, 50 per cent in the second hour, 50 per cent in the third hour, 40 per cent in the fourth hour and 27 per cent in the fifth hour. This curve, and the zone above, may be considered as indicating the range of values for schizophrenia, characterized by overproduction of an anti-insulinic factor. A negative reaction to the test does not necessarily exclude the presence of schizophrenia, but a positive reaction in conjunction with the clinical picture substantiates its presence.

In connection with our results we should call attention to the work of Banting, Franks and Gairns.[2] These authors found in 1 case of schizophrenia, in which unusually large doses of insulin were used in treatment, that the patient became resistant to insulin. The blood

2. Banting, F. G.; Franks, W. R., and Gairns, S.: Anti-Insulin Activity of Serum of Insulin-Treated Patient, Am. J. Psychiat. **95**:562, 1938.

obtained from this patient contained an anti-insulinic factor. They suspected the "relation of a possible pituitary dysfunction to the clinical picture."

Though the presence of an anti-insulinic factor in a patient treated with an enormous amount of insulin (up to 1,000 units in one dose) cannot be considered conclusive evidence of the relation of pituitary dysfunction to the clinical picture, our experiments carried out with untreated patients' blood have only confirmed the suspicions of Banting and his co-workers. The fact that our test gave a positive result in 1 case of gross anatomic pituitary disease confirms the hypothesis that the factor concerned is of pituitary origin. This assumption is further corroborated by the work of Karelitz, Cohen and Leader,[3] who with the same method found an inhibitory effect of the serum of diabetic subjects on the effect of insulin. Further work will demonstrate whether or not the same reaction is associated with other diseases. The differentiation of gross disease of the pituitary in the ordinary sense and diabetes of pituitary origin accompanying schizophrenia presents no difficulty clinically and should not disturb the usefulness of this test in the diagnosis of schizophrenia.

At present we are not able to determine the malignancy of these forms of schizophrenia. Neither is it possible to reach conclusions as to the relation of remissions occurring spontaneously or as the result of treatment to the two forms of schizophrenia here indicated. Here is a broad field for investigation.

SUMMARY

Substantiation of a biochemical disturbance in schizophrenia has been presented. This disturbance indicates the presence of an anti-insulin substance in the blood of schizophrenic patients.

This disturbance or the failure of the organism to adjust this disturbance may be one of the etiologic factors in schizophrenia.

A blood sugar curve has been plotted which under the experimental conditions outlined is possibly significant for one form of schizophrenia and may be used as a biologic test.

A subdivision of schizophrenia into two pathogenically different forms is indicated.

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3. Karelitz, S.; Cohen, P., and Leader, S. D.: Studies on Inhibition of Insulin Activity, Proc. Soc. Exper. Biol. & Med. **26**:11, 1928.

CONTINUOUS AMBULATORY INSULIN SHOCK TECHNIC IN TREATMENT OF SCHIZOPHRENIA

REPORT OF TWO CASES

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In 1940, in describing our ambulatory insulin shock technic for patients with mental disorders, we [1] reported that 81 per cent of such patients who were treated with mild daily hypoglycemic shocks over a period of several months showed definite clinical improvement. The most marked improvement was observed in patients with schizophrenia. This observation was recently confirmed.[2]

The view was expressed that it might be necessary to treat certain patients with mild daily hypoglycemic shocks for an indefinite period in order to maintain clinical improvement. The present report deals with the cases of 2 patients with schizophrenenia treated with the ambulatory insulin shock technic over a period of two and a half years, in 1 case, and one and a fourth years in the other.

TECHNIC OF THE AMBULATORY INSULIN TREATMENT

The patients received one hypodermic injection of insulin daily at 5 a. m. and when, several hours later, hypoglycemic symptoms had been present for one-half hour orange juice or sugar water was given and then the usual hospital breakfast. The initial dose of insulin was generally 5 units. This was increased daily until the patients manifested mild hypoglycemic shock, usually characterized by weakness, excessive perspiration and some drowsiness. As a general rule, 40 units of insulin in one dose was sufficient to produce the desired effect within five hours. During the hypoglycemia the patients were up and about, mingling with the others and attending to their routine ward duties. If they complained

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From the Department of Psychiatry, New York State Psychiatric Institute and Hospital.

1. Polatin, P.; Spotnitz, H., and Wiesel, B.: Ambulatory Insulin Treatment of Mental Disorders, New York State J. Med. **40**:843-848 (June 1) 1940.

2. Tomlinson, P. J., and Ozarin, L. D.: Ambulatory Insulin Therapy: Report of Fifty-Two Cases, read at the Inter-Hospital Conference of the New York "Up-State" Hospitals, Utica, N. Y., April 25, 1941.

of weakness and preferred to remain in bed, they were permitted to do so during the one-half hour of manifest hypoglycemic symptoms. The mild hypoglycemic symptoms usually did not prevent the patients from feeding themselves at breakfast without assistance. Only rarely was it necessary to urge them to eat.

REPORT OF CASES

CASE 1.—B. K. is a 28 year old single white woman whose illness began in May 1931, while a student at a university. After recovering from an attack of jaundice, she became worried about having fallen behind in her work, feared that she would not pass and became self accusatory and depressed. Gradually she grew excited and incoherent and presented auditory, visual and olfactory hallucinations, with rare lucid intervals. At other times she was preoccupied and retarded and refused food.

She was first admitted to the New York State Psychiatric Institute on June 30, 1931, with a diagnosis of dementia praecox, hebephrenic type. Physically she was in good condition. After a year in the hospital she was discharged without any evidence of improvement. Her condition remained unchanged until December 1936, when she was readmitted to the Psychiatric Institute for a course of insulin coma treatments (Sakel technic). With this therapy there was a remission, but after eight months she relapsed. Another course of insulin coma therapy followed, without any change in her condition, but a course of metrazol treatments resulted in remission. After a month, however, she again relapsed and was then placed under combined insulin and metrazol therapy. During this procedure, in September 1938, a pulmonary abscess developed, after aspiration of vomitus. Two months later, in November, while the patient was still severely ill, both physically and mentally, the ambulatory insulin therapy was instituted, and this is being continued up to the present time, a period of approximately two and a half years.

The patient has had 755 treatment days, resulting in 600 mild hypoglycemic shocks. The insulin was gradually increased to 50 units daily in the first six months, and then, as the patient acquired a sensitivity to the substance, the dose was gradually diminished, so that she reacted as well to 25 units daily. This is her present dose. She has received a total of 32,500 units of insulin since the beginning of ambulatory insulin treatment.

In less than a month after institution of this form of insulin treatment the patient began to show definite gain in weight, and during the subsequent year she gained more than 50 pounds (22.7 Kg.). In December 1939 she weighed 154 pounds (69.9 Kg.). She voluntarily began to reduce and was encouraged to do so. She lost 38 pounds (17.2 Kg.) and now weighs 116 pounds (52.6 Kg.). Signs and symptoms of pulmonary abscess have disappeared. In 1940 roentgenograms of the chest showed only a residual increase in the bronchovascular markings in the right lower lung field, the site of the original abscess. There has been no change on roentgen examination during the past year.

When the ambulatory insulin therapy was initiated the patient was in a state of mental deterioration. She was generally confused, out of contact and hallucinating and assumed various stereotyped and catatonic postures. Gradually, over an interval of a year, she began to show longer and longer daily periods of improvement after the insulin shock, so that the schizophrenic behavior pattern disappeared and was evident only when she was crossed in her demands, and then to a milder degree. Otherwise, she was in good contact, pleasant, able to leave the hospital for short excursions and appeared to have made a good social

recovery. There was, however, a large element of compulsive activity as a residual factor. During the past year her state of improvement has been enhanced. In February 1941, with the dose of insulin reduced to 15 units and no hypoglycemic reactions, the patient showed a tendency to stereotypy, with posturing and inappropriate affect. All this disappeared when the dose was increased to 25 units and hypoglycemic reactions were obtained. At present she is in a state of good social remission, with some compulsive features and a superficial lability of affect.

The laboratory data in April 1941 were as follows: The blood count, results of urinalysis and chemical constituents of the blood were all within normal limits. The fasting blood sugar was 84 mg. per hundred cubic centimeters. The sedimentation rate was 16 mm. per hour. The electroencephalogram was interpreted as follows: "The character of the record is suggestive of a mild degree of electrocortical dysfunction over the anterior region bilaterally, more so on the right than on the left. In addition, the low voltage pattern plus the low alpha incidence might be associated with active preoccupation on the part of the patient."

The psychologic report on April 1, 1941 was as follows: "The Wechsler-Bellevue scale reveals an intelligence quotient of 114, a rating which indicates a high average intelligence. There is no impairment in capacity for conceptual thinking. A tendency toward distraction to irrelevant details is noted throughout the examination."

CASE 2.—S. G. is a 22 year old single white woman whose illness began in September 1939 with marked preoccupation, bizarre delusions, incoherent, incessant chatter and inappropriate smiling and laughter.

She was admitted to the Psychiatric Institute on Oct. 6, 1939, with a diagnosis of dementia praecox, hebephrenic type. Although poorly nourished, she was in good physical condition. In December 1939, and for a subsequent period of about nine weeks, she received the ambulatory insulin treatment, but with no favorable effects.

In April 1940, and for a subsequent period of ten weeks, the patient was placed on insulin coma therapy (Sakel technic). This resulted in aggravation of her mental condition, so that it was necessary to transfer her to the service for disturbed patients.

In July 1940 the patient was again placed on ambulatory insulin therapy, this being continued up to the present time, a period of about ten months. With this course she has now had 181 treatment days, resulting in 175 mild hypoglycemic shocks. The insulin was gradually increased to 50 units daily in the first three months, and then as the patient acquired sensitivity to the substance, the dose was gradually diminished, so that she reacted as well to 25 units daily. Then as tolerance to the insulin developed, the dose was increased to 35 units, to which dose she is reacting at present. During this course, she has now received a total of 6,355 units of insulin.

About seven weeks after the beginning of this course of treatment the patient began to show evidence of improvement for short periods. Gradually, it was observed that these short periods of improvement were coalescing, so that a more acceptable response was evident over a longer period each day.

About seven months after the initiation of this therapy the patient was sustaining her improvement, and ten months after the beginning of treatment it was considered that she had returned to her premorbid mental level and behavior.

The laboratory data in April 1941 were as follows: Urinalysis, hematologic studies and chemical determinations on the blood all gave results within normal limits. The sedimentation rate was 17 mm. per hour; the fasting blood sugar was 90 mg. per hundred cubic centimeters, and the basal metabolic rate was

—9 per cent. The electroencephalogram was interpreted as indicating no electrocortical dysfunction.

On physical and neurologic examination no abnormalities were found.

A recent psychometric examination revealed an intelligence quotient of 101. Verbal and performance materials were handled with equal facility. Supplementary tests showed that the patient was functioning consistently at the intellectual level of the average adult.

COMMENT

It is of considerable interest that both these patients presented a common feature, namely, that under continued treatment with mild insulin shock, mental improvement occurred and could be appreciated only after a long period. Definite clinical improvement was not observed until the patients had been under treatment for about a year. It is noteworthy that after long-continued ambulatory insulin therapy both patients showed average intelligence on psychometric examinations, with no observable evidence of intellectual deterioration. This is particularly significant in the case of B. K. who has had schizophrenia for ten years.

Ambulatory insulin treatment of schizophrenia seems to produce a gradual physiologic change, and it is only after many repeated mild hypoglycemic shocks that the patient begins to show definite mental improvement. Sensitivity to insulin increases as the treatment progresses.

The mental improvement observed appears to bear a definite relation to the mild hypoglycemic shocks produced by insulin, since there is a tendency to relapse when insulin is discontinued or when the dose is insufficient to produce hypoglycemia. This would seem to indicate that in some cases of chronic schizophrenia ambulatory insulin treatment is necessary for an indefinite period, or for the remainder of the patient's life. From a study of these 2 cases there does not seem to be any harmful effect from the long-continued use of insulin.

CONCLUSIONS

The cases of 2 patients with schizophrenia treated with the ambulatory insulin shock technic are reported. The first patient has been treated for two and a half years; the second, for a year and three months. Both patients are still being treated and have manifested marked clinical improvement.

Definite clinical improvement could be observed only after the patients had been treated with mild daily hypoglycemic shocks for many months.

The beneficial effects of these shocks appeared to be cumulative.

Evidence in case 1 demonstrated that when the dose of insulin was insufficient to produce a mild hypoglycemic shock a relapse occurred.

It is recommended that patients with chronic schizophrenia of long standing be treated with mild daily hypoglycemic shocks for an indefinite period in order to obtain and to maintain clinical improvement.

CEREBRAL FAT EMBOLISM

A CLINICOPATHOLOGIC STUDY OF TWO CASES

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Fat embolism is by no means a new subject. This is evident from even a superficial search through the literature, which discloses over 500 references. In spite of this voluminous literature, the condition is rarely diagnosed intra vitam, and only when the symptoms are severe is it even suspected. More recent neurologic textbooks either omit the subject entirely or make but scant mention of it. With increase in the number of fractures of long bones and trauma to fat deposits, as a result of automobile accidents, there has been an increase in the number of cases of fat embolism.

Cerebral fat embolism is usually but one of the components of a universal fat embolism. Its clinical picture is frequently only the final episode in the story. The cerebral involvement usually dominates the clinical picture, and the pulmonary symptoms may escape detection.

The literature on fat embolism dates back many years. As early as 1669 Lower [1] reported his experiments with intravenous injections of milk into dogs. Over one hundred and fifty years later Magendie (1821 to 1836)[2] injected olive oil directly into the blood stream of animals, causing death in a few minutes from asphyxia and pulmonary edema. He attributed death to increase in the viscosity of the blood, producing occlusion of the smaller vessels. Zenker (1862)[3] first described fat emboli in the human pulmonary capillaries after a crushing injury to the chest. Wagner (1865)[4] attempted to delineate a clinical syndrome on the basis of a study of 48 cases of fat embolism in man. Von Bergmann (1863)[5] is credited with making the first

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1. Lower, R.: Tractatus de corde, London, J. Allestry, 1669.

2. Magendie, F.: Sur da circulation du sang, J. de physiol. expér. **1**:37, 1821.

3. Zenker, F. A.: Beiträge zur normalen und pathologischen Anatomie der Lunge, Dresden, J. Braunsdorf, 1862, p. 31.

4. Wagner, E.: Die Fettembolie der Lungen-Capillaren, Arch. f. Heilk. **4**:146, 369 and 481, 1865.

5. Bergmann, E. B.: Zur Lehre von der Fettembolie, Inaug. Dissert., Dorpat, E. J. Karow, 1863.

clinical diagnosis of fat embolism in man. Scriba's work (1880)[6] has been the basis of most of the statements in the "modern" textbooks and literature, even though many of his opinions have been proved to be erroneous. According to Gauss,[7] the original description of cerebral fat embolism in America was given by Fenger and Salisbury (1879).[8] Groskloss [9] provided an excellent summary of the literature up to 1935 and a detailed description of the entire problem of fat embolism.

An advance in knowledge of the clinical aspect of cerebral fat embolism was made by Hämig (1895-1900),[10] who stressed the constancy of the "free interval," lasting from six to eight hours, followed by delirium, stupor, coma, rising temperature and death within six days. He found emboli in all viscera, especially the heart, and expressed the opinion that "cardiac paralysis" could occur. He discovered fat in the urine in the absence of definite cerebral symptoms and claimed that the major circulation, including that of the brain, might contain fat in quantities too small to disturb function.

It was not until 1913 that the first important American contribution was published by Warthin,[11] whose paper contained not only an extensive review of the literature with a condensed protocol of 15 typical cases but his own experimental results. He attempted to establish a definite symptom complex out of a mass of conflicting statements. He described a new clinical sign—"the presence of free fat and fat-granule alveolar cells in the sputum"—as the "earliest positive evidence" of fat embolism. He claimed that in fat embolism no organ escapes having some fat in its capillaries. The heart and lungs bear the original brunt of the damage. When the fat suddenly enters the blood stream the effect on the heart may be the same as that of an air embolus. The heart action may be impeded not only by fat in its own vessels but by inability to force the blood through the lungs. Warthin described small perivascular hemorrhages surrounded by necrotic tissue in the brain. He expressed the belief that cases of mild and recoverable fat embolism are

6. Scriba, J.: Untersuchungen über die Fettembolie, Deutsche Ztschr. f. Chir. **12**:118, 1880.

7. Gauss, H.: Studies in Cerebral Fat Embolism with Reference to the Pathology of Delirium and Coma, Arch. Int. Med. **18**:76 (July) 1916.

8. Fenger, C., and Salisbury, J. H.: Diffuse Multiple Capillary Fat Embolism of the Lungs and Brain as a Fatal Complication in Common Fractures, Illustrated by a Case, Chicago M. J. **39**:587, 1879; M. Rec. **17**:127, 1880.

9. Groskloss, H. H.: Fat Embolism, Yale J. Biol. & Med. **8**:59 and 175, 1935; **8**:297, 1936.

10. Hämig, G.: Ueber die Fettembolie des Gehirns, nach klinischen Beobachtungen, Beitr. z. klin. Chir. **27**:333, 1900.

11. Warthin, A. S.: Traumatic Lipaemia and Fatty Embolism, Internat. Clin. **4**:171, 1913.

very common and that fatal cases are more numerous than is suspected. He claimed that the prognosis is grave when the signs and symptoms are pronounced enough to be recognized.

PATHOGENESIS

Explanation of the mechanism of fat embolism has given rise to a voluminous literature, much of which is confusing and contradictory. The fat may have either an endogenous or an exogenous source. Endogenous fat would include fat from bone marrow, subcutaneous tissue, parenchymatous organs and lipemic states complicating diabetes, narcosis (Lehman and Moore [12]) or following a fatty meal (Neumann [13]). Leathes and Raper [14] concluded that not all fat embolism is traumatic in origin but that under abnormal conditions fat can be liberated from its normal emulsified state. These authors gave ether by the intravenous and inhalation routes to starved and to well fed dogs. The starved dogs showed no evidences of fat embolism, but in the well fed dogs lipemia with fat emboli in the lungs resulted, especially in the animals to which the ether was given by inhalation. They concluded that death after prolonged ether anesthesia was probably the result of fat embolism; they expressed the belief that starvation prior to operation may prevent fat embolism.

Wüttig [15] produced pulmonary embolism in rabbits with excessive feeding of cod liver oil. Lehman and Moore [12] showed in animals and in the test tube that some of the fat is derived from the blood itself. There is much in favor of the opinion that the fat is caused to fuse into large globules from the minute particles in which it normally existed in the blood. The hypothesis is plausible in view of the presence of large amounts of fat in the lungs and brain following relatively mild injury or fracture of the smaller bones of the body.

The exogenous source of fat, therapeutic injections of fatty substances, is much less important.

Method of Transportation of the Fat.—Experimental work has also concerned itself with this problem. Busch [16] injected olive oil, colored with cinnabar, into the tibial marrow of rabbits and subsequently found the particles in the pulmonary tissues. Because the lymphatics and

12. Lehman, E. P., and Moore, R. M.: Fat Embolism Including Experimental Production Without Trauma, Arch. Surg. **14**:621 (March) 1927.

13. Neumann, A.: Ueber die Beobachtung des resorbierten Fettes im Blute mittels des Ultra-Condensors, Zentralbl. f. Physiol. **21**:102, 1907.

14. Leathes, J. B., and Raper, H. S.: The Fats, ed. 2, London, Longmans, Green & Company, 1925, p. 144.

15. Wüttig, H.: Experimentelle Untersuchungen über Fettaufnahme und Fettablagerung, Beitr. z. path. Anat. u. z. allg. Path. **37**:378, 1905.

16. Busch, F.: Ueber Fettembolie, Virchows Arch. f. path. Anat. **35**:321, 1866.

glands contained such small amounts of the material he concluded that the veins act as the avenues of transportation. Wiener [17] found fat emboli in the lungs after intraperitoneal and intrapleural injections of fat. Fritzsche [18] ligated the lymphatics draining the extremities of half of his experimental animals. After percussing the tibias of all the animals he found fat emboli in both the ligated and the nonligated extremities.

Gröndahl [19] ligated both the venous and the lymphatic drainage of the extremities of experimental animals, and fat embolism occurred. Lehman [20] maintained that "no fracture is apt to disorganize all the marrow fat cells of a bone." He asserted that it is impossible to explain the forcing of fat into the veins. "The course of the venous current above an injury is away from the site of injury, yet the pressure in the vein is a positive and not a negative pressure." The veins (except in the thorax) exert no suction at any time, even immediately after injury. He claimed that at this time all currents lead toward, and not away from, the line of fracture. Lehman concluded that "(1) fat in quantities can hardly enter damaged veins, and (2) that fat in sufficient quantity to cause symptoms and death is rarely liberated by trauma."

After the fat enters the circulation its course is more certain than its origin or method of conveyance. The initial arrest of the fat particles takes place in the lungs, "the guardian angel of the systemic circulation." It has been claimed that two routes are available for the fat to enter the systemic circulation (Vance [21]): (1) through the pulmonary capillaries and (2) through an open foramen ovale. Case reports have been given to substantiate both sides of the controversy. Fuchsig [22] reported a case in which there was an open foramen ovale with pulmonary fat embolism. On the other hand, cases have been reported in which fat was present in the urine and the lungs were entirely free and only the systemic circulation contained fat emboli.

Prevention and Therapy.—These problems have not been neglected in the experimental field. Stress has been placed, however, on prevention rather than therapy. The avoidance of unnecessary handling or

17. Wiener, M.: Wesen und Schicksal der Fettembolie, Arch. f. exper. Path. u. Pharmakol. **11**:275, 1879.

18. Fritzsche, E.: Experimentelle Untersuchungen zur Frage der Fettembolie mit spezieller Berücksichtigung prophylaktischer und therapeutischer Vorschlage, Deutsche Ztschr. f. Chir. **107**:456, 1910.

19. Gröndahl, N. B.: Untersuchungen über Fettembolie, Deutsche Ztschr. f. Chir. **111**:56, 1911.

20. Lehman, E. P.: Fat Embolism, Internat. S. Digest **7**:131, 1929.

21. Vance, B. M.: The Significance of Fat Embolism, Arch. Surg. **23**:426 (Sept.) 1931.

22. Fuchsig, E.: Ueber experimentelle Fettembolie, Ztschr. f. exper. Path. u. Therap. **7**:702, 1910.

rough manipulation of a fracture or of bone at operation is said to be an important factor in the prevention of fat embolism. Ryerson [23] advised the use of Esmarch's tourniquet in cases of fractures or bone operation, in view of the experiments showing that its gradual release after manipulation or operation greatly lessened the amount of fat embolism in experimental animals (Caldwell and Huber [24]). Other preventive measures have included drainage of the area of fracture with evacuation of blood and fat, drainage of the thoracic duct in the neck (Wilms [25]; Fritzsche [18]), venesection to remove some of the fat within the circulating blood (Czerny [26]) and the avoidance of ether anesthesia (Lehman and Moore [12]). Gröndahl,[19] however, noted that even ligation of the femoral vein and removal of the inguinal glands did not prevent fat embolism.

As far as therapy itself is concerned, both surgical and medical measures have been proposed. The object of treatment has been either to dissolve the fat or to reduce it to such fine droplets as to permit them to pass through the pulmonary filter for excretion by the kidneys. The well known fat solvents and emulsifiers have failed to accomplish this in the experimental animal. Rappert [27] has made use of decholin sodium (the sodium salt of dehydrocholic acid) plus circulatory stimulants and a preparation of papaverine. He claimed that he was able to save experimental animals by this therapy after injection of several times the usual fatal dose of fat. The following routine of treatment has been developed by this author: A drip infusion is instituted, and decholin sodium is administered in large doses (from 200 to 300 cc. of a 20 per cent solution daily). The effect can be enhanced by the addition of a 25 per cent solution of pyridine betacarbonic acid diethylamine, metrazol or other drugs. The preparation of papaverine is said to dilate the pulmonary capillaries and to increase the efficiency of the therapy. The decholin will often produce icterus for twenty-four to forty-eight hours. According to Rappert, only 2 per cent of 49 patients who received this therapy survived and 35 per cent of 20 patients so treated survived.

Interpretation of the Microscopic Presence of Fat Embolism in the Lungs.—Great caution must be exercised in evaluating the significance of pulmonary fat embolism. A routine search for this condition has

23. Ryerson, E. W.: Fat Embolism in Bone Surgery: Incidence and Prevention, J. A. M. A. **67**:657 (Aug. 26) 1916.

24. Caldwell, G. T., and Huber, H. L.: Fat Embolism Following Trauma to Bones, Surg., Gynec. & Obst. **25**:650, 1917.

25. Wilms, M.: Traitement de l'embolie graisseuse par drainage temporaire du canal thoracique, Semaine méd. **30**:138, 1910.

26. Czerny, V.: Ueber die klinische Bedeutung der Fettembolie, Berl. klin. Wchnschr. **12**:593, 1875.

27. Rappert, E.: Fettembolie und ihre Behandlung, Deutsche Ztschr. f. Chir. **250**:276, 1938; abstracted, J. A. M. A. **111**:212 (July 9) 1938.

revealed an amazingly high incidence. Dietrich [28] claimed that only when more than two thirds of the entire lung is involved by fat embolism is the diagnosis justified. Hoffheinz [29] asserted that the so-called postmortem fat embolism must be ruled out, since putrefactive processes can produce postmortem migration of fat. As early as 1898 Carrara [30] observed fat embolism in 22 per cent of cases of death from cardiovascular-renal disease and in 44 per cent of cases of death from burns. Scuderi [31] found fat within the pulmonary capillaries in 50 per cent of unselected cadavers. Lehman and Moore [12] found fat embolism in 74 per cent of unselected lungs. These observations have been confirmed by Wright,[32] who found that 52 of 100 consecutive patients examined post mortem had pulmonary fat embolism, the majority of whom did not suffer from fracture or contusion.

Excretion of Fat.—The excretion of fat once the blood stream has been invaded has been the subject of much study. The first attempt at localization of the process is in the pulmonary capillaries. That this arrest of the fat droplets is by no means complete is shown by the invasion of the systemic circulation. Gröndahl [19] observed a higher incidence of invasion of the greater circulation in persons possessing good myocardial musculature. This has been explained by the force necessary to push the particles through the vessels of the lesser circulation. That the fat does get into the major circulation is shown by the presence of fat in the urine and in the sputum. Scriba (1880)[6] reported the presence of fat in the urine of 80 per cent of his cases two to six days after fracture or bone operation. He found that it may disappear suddenly, to make its appearance again in from eight to thirteen days. There may be three or four such excretory cycles. Another means of excretion of fat is through the pulmonary alveoli (Warthin [11]; Lehman and McNattin [33]). The latter did not consider Warthin's sign (fat in the sputum) pathognomonic but expressed the belief that fat can occur in the air spaces of the lung without fat embolism.

SYMPTOMATOLOGY

Attempts to establish a characteristic symptom complex date back many years. The pulmonary symptom complex was described as early

28. Dietrich, A.: Die Bewertung der Fettembolie, Chirurg **2**:593, 1930.

29. Hoffheinz, cited by Groskloss.[9]

30. Carrara, M.: Ueber die Fettembolie der Lungen in ihren Beziehung zur gerichtlichen Medicin, Friedreichs Bl. f. gerichtl. Med. **49**:241, 1898.

31. Scuderi, C. S.: Fat Embolism: Résumé of the Literature Plus Some Newer Thoughts on Diagnosis, Arch. Surg. **36**:614 (April) 1938.

32. Wright, R. B.: Fat Embolism, Ann. Surg. **96**:75, 1932.

33. Lehman, E. P., and McNattin, R. F.: Fat Embolism: II. Incidence at Postmortem, Arch. Surg. **17**:179 (Aug.) 1928.

as 1898 by Payr.[34] Since then cardiac, renal and cerebral symptom complexes have been recorded. Such clearcut textbook divisions, however, are not always possible. The most important single symptom is the so-called free interval. Following the injury there is a constant period of freedom from all symptoms, varying from hours to days (three to six days is the average). The shortest interval, thirty minutes, was reported by Bürger[35]; the longest, nine days, by Hahn.[36]

The second fairly constant sign is a rise in body temperature. However, a fall in temperature has been reported by several investigators (Scriba[6]; Meeh 1892[37]).

As a rule the disease is ushered in by pulmonary symptoms including dyspnea, pain in the chest, cyanosis, cough, increase in pulse rate and restlessness. The diagnosis of bronchopneumonia may be made at this time by the unwary. Great strain is thrown on the heart, with gradual weakness in cardiac power, increase in pulse rate, fall in systolic pressure and rise in venous pressure.

The brain is usually the first organ to announce the invasion of the greater circulation by fat particles. The pulmonary symptoms have been absent in about one third of the cases, as shown by the studies of Strauss (1933).[38] The earliest cerebral manifestations are insomnia, delirium, disorientation and cortical irritative phenomena, consisting of convulsions, rigidity or, rarely, focal symptoms. There follows stupor rapidly increasing to coma. Death usually takes place within three to four days. There are rarely signs of increased intracranial pressure, and the spinal fluid in nearly all cases has been entirely normal. The urine (Jirka and Scuderi[39]) and sputum have shown fat droplets. In examining the urine for fat the bladder must be completely emptied, by catheter if necessary, because the fat rises to the top in watery solutions. The diagnostic importance of lipuria has given rise to considerable discussion. Some have expressed the belief that lipuria is not always diagnostic of fat embolism (Scriba[6]; Killian[40]). Others (Strauss[38];

34. Payr, E.: Weitere Beiträge zur Kenntnis und Erklärung des fettembolischen Todes nach orthopädischen Eingriffen und Verletzungen, Ztschr. f. orthop. Chir. **7**:338, 1900; München. med. Wchnschr. **45**:885, 1898.

35. Bürger, L.: Die Bedeutung der Fettembolie für den Kreigschirurgen, Med. Klin. **11**:996, 1915.

36. Hahn, cited by Groskloss.[9]

37. Meeh, K.: Tödliche Fettembolie nach Frakturen, Beitr. z. klin. Chir. **8**: 421, 1892.

38. Strauss, A.: Cerebrale Fettembolie, Zentralbl. f. d. ges. Neurol. u. Psychiat. **66**:385, 1933.

39. Jirka, F. J., and Scuderi, C. S.: Fat in Urine, J. Lab. & Clin. Med. **20**: 631 and 945, 1935.

40. Killian, H.: Die traumatische Fettembolie, Deutsche Ztschr. f. Chir. **231**: 97, 1931.

Elting and Martin [41]) have stated that lipuria is diagnostic and that even if the clinical syndrome is not fully developed or characteristic fat embolism exists in a mild and recoverable form. While theoretically lipuria can occur in conditions other than fat embolism, such as the lipemia of diabetes, its occurrence should make one consider the possibility of fat embolism.

Warthin,[11] as has been mentioned, stressed the importance of fat in the sputum in the form of droplets of free fat or within phagocytes in cases of fat embolism. He claimed that this finding was of greater importance than lipuria because it is more constant and earlier in appearance.

Free fat in the blood has not been considered of great diagnostic importance. The amount of fat has been thought of less importance than the presence of large fat globules within the blood stream.

Cutaneous hemorrhages have been reported and are supposedly characteristic (Benestad [42]; Busch [16]; Killian [40]). While they may appear within twelve hours after the accident (Warthin [11]), they usually are not evident before the third day of the illness. They occur mainly on the abdomen, chest, shoulders and upper extremities and do not disappear on pressure.

REPORT OF CASES

CASE 1.—J. F., a 48 year old white man, became depressed in May 1937. On April 15. 1938, at 1:45 a. m., he jumped out of a second story window to a concrete pavement below. There were laceration of the scalp in the occipital area, crepitus over the ilium and eversion of the right lower limb. He was conscious and not in shock and showed no evidence of internal bleeding.

The patient was taken by ambulance to the Jewish Hospital, a distance of only a few miles, and was brought directly to the x-ray room. Studies showed a fracture in the lower third of the right femur and a comminuted fracture of the ilium. He was removed to his room, and extension was applied (Dr. Norman Rothschild). The patient seemed to be in good condition during that entire day. His temperature was moderately elevated, but the pulse was not rapid. During that night he was clear mentally. He was unable to sleep, however, and morphine was given. At 11 a. m. the next morning the patient was comatose and had stationary, pinpoint pupils, Cheyne-Stokes respiration, increased reflexes and a Hoffmann sign bilaterally. There was no Babinski sign or rigidity of the neck. He died April 18, about sixty hours after the injury.

During the last few days of the patient's illness the temperature mounted steadily and reached 106 F. on the day of his death. The pulse rate rose proportionately and for twenty-four hours before death could not be counted; the respiratory rate reached 45 per minute on the day of death.

Gross Examination of the Brain.—On removal of the brain a thin film of blood was noted under the dura; this could be washed off easily. There was no evidence of fracture of the skull.

The brain itself, which was of normal size, was unusually tense and showed congestion. There was terminal thrombosis of some of the large veins entering

41. Elting, A. W., and Martin, C. E.: Fat Embolism, Ann. Surg. **82**:336, 1925.

42. Benestad, G.: Drei Fälle von Fettembolie mit punktförmigen Blutungen in der Haut, Deutsche Ztschr. f. Chir. **112**:194-205, 1911.

the superior longitudinal sinus. The large blood vessels showed no evidence of sclerosis or fibrosis.

Pinpoint areas of softening were noted in the basal portion of the pons. The ventricles were moderately dilated. The corpus callosum was of normal thickness. The cortex showed only mild congestion. Throughout the white matter petechiae were noted, some of which were larger than the head of a pin, but for the most part they were small and widely scattered.

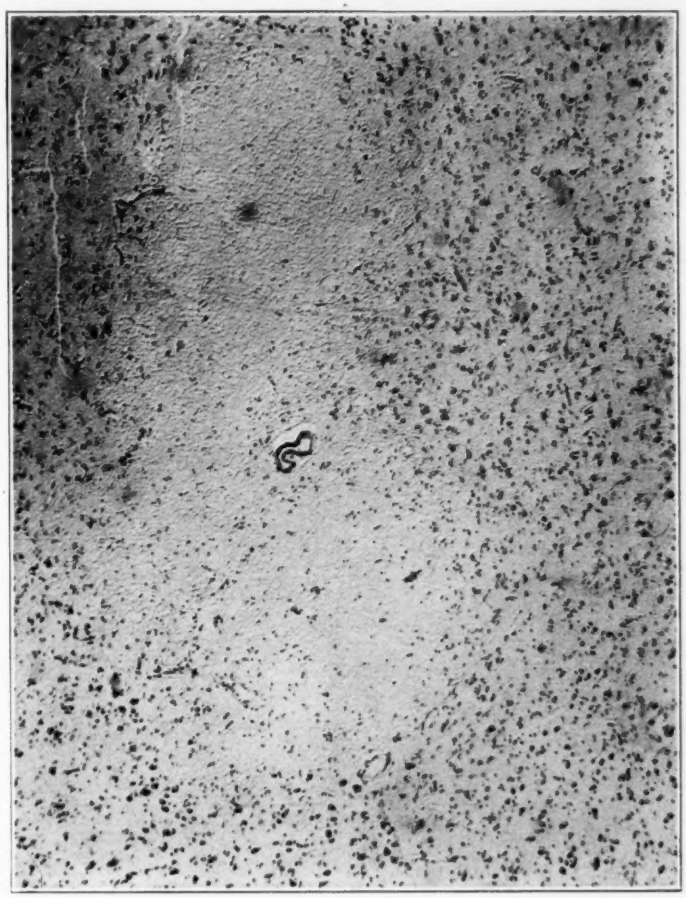

Fig. 1 (case 1).—Cerebral cortex, showing two acellular areas which have become fused. The mechanism of vascular occlusion is not demonstrable with a cell stain. Toluidine blue stain; alcohol fixation; pyroxylin embedding.

Microscopic Examination of the Brain.—The subarachnoid space was dilated and contained small amounts of debris and phagocytic elements, without inflammatory reaction.

The cortex showed many areas of complete cellular destruction, mainly around the small vessels (fig. 1), without glial reaction surrounding them. The ganglion cells at the periphery of these areas were devoid of Nissl bodies, and the nuclei

tended to assume an eccentric position. Naked ganglion cell nuclei could also be seen; other cells had undergone liquefaction necrosis.

The subcortex showed irregularly distributed areas of necrosis (fig. 2) and small petechiae. Sommer's sector was not involved. The basal ganglia, midbrain, pons and white matter of the cerebellum revealed areas of destruction and hemorrhage similar to those in the subcortex.

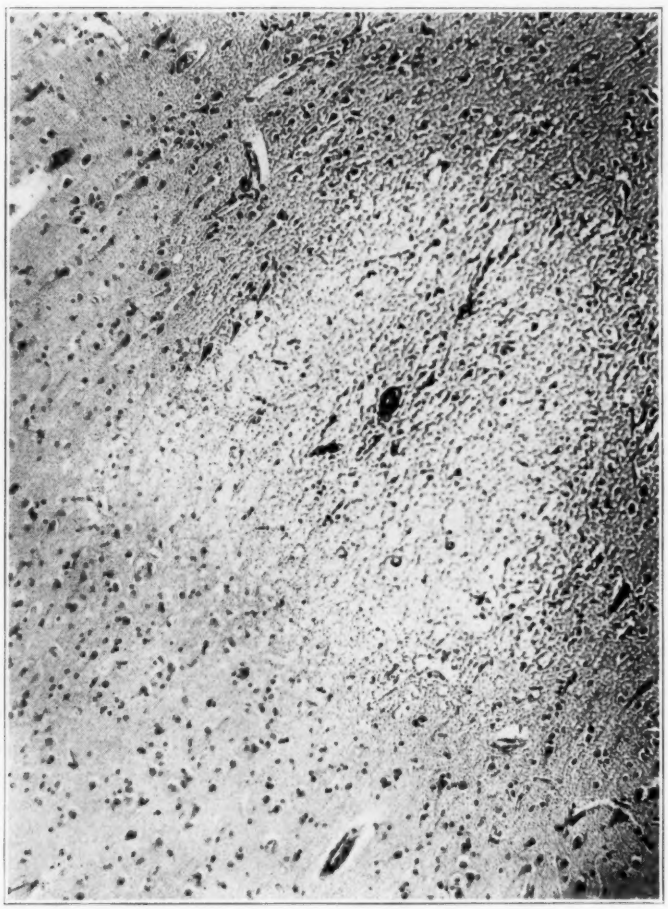

Fig. 2 (case 1).—Corticosubcortical margin, showing area of necrosis with status spongiosus, without glial proliferation or vascularization. The central vessel is prominent. Toluidine blue stain.

Myelin sheath stains revealed the degenerated areas to be demyelinated foci, occurring mainly around the smaller blood vessels (fig. 3 *A* and *B*). Some were fused and formed larger, irregular demyelinated islands, mainly within the white matter.

The scarlet red stain showed that many of the precapillary and capillary vessels of both cortex and subcortex were occluded by fat globules (fig. 4 *A*). The occluded vessel was often in the center of the area of demyelination (fig. 4 *B*).

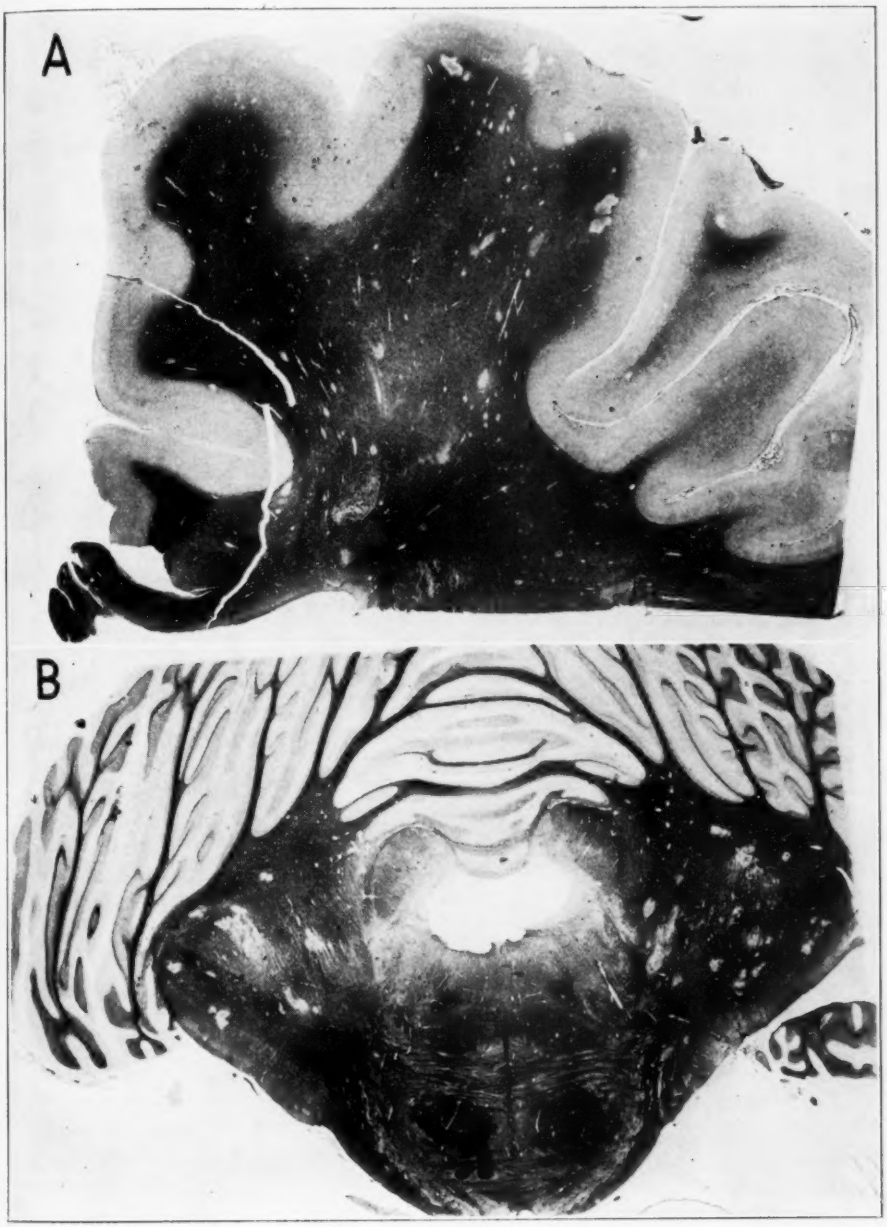

Fig. 3 (case 1).—*A*, frontal lobe, showing numerous areas of degeneration of varying sizes in both cortex and subcortex, especially the latter.

B, pons, showing numerous small demyelinated areas, mainly in the middle cerebellar peduncles.

Weil myelin sheath stain.

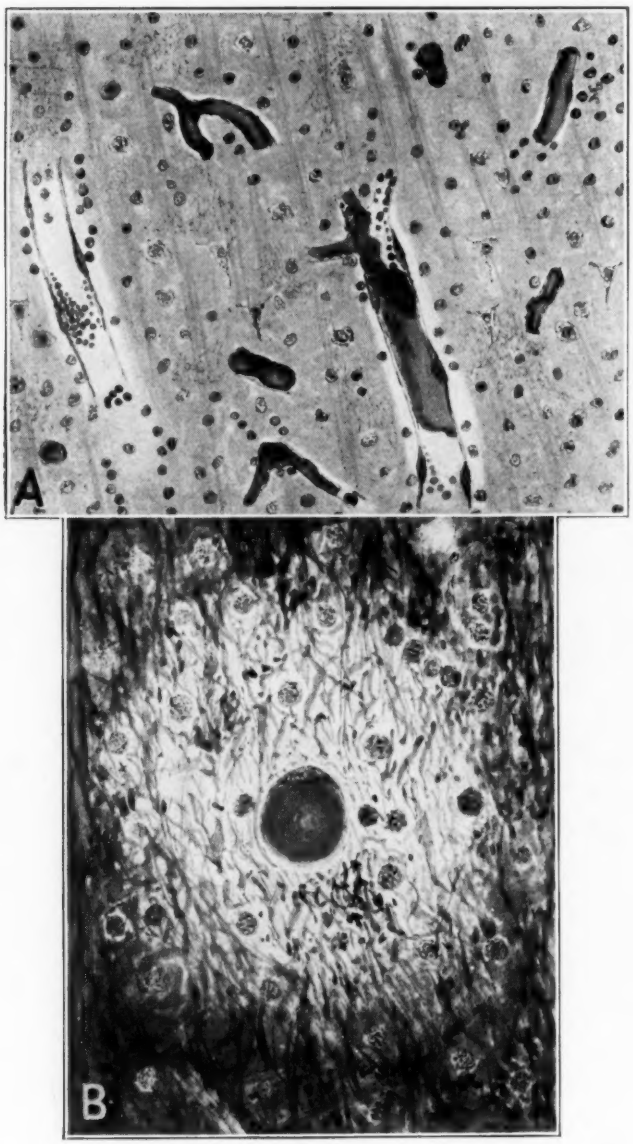

Fig. 4 (case 1).—*A*, cortex showing fat within the blood vessels.

B, subcortex, showing small vessel completely occluded by a large fat globule with small perivascular area of degeneration.

Scarlet red stain; drawn by Dr. M. T. Moore.

Fat-filled vessels were also found throughout the basal ganglia, the brain stem and the white matter of the cerebellum. Not all the small vessels were occluded, nor did they all contain fat. This was in keeping with the irregular distribution of the acellular areas within the cortex and the demyelinated areas within the subcortex. The larger blood vessels as a rule did not contain fat.

Bielschowsky preparations showed axon degeneration within these foci. Swollen, fragmented and tortuous axons passed through the foci of demyelination.

The large blood vessels were well preserved, the medium-sized vessels showed no hyalinization and the smaller ones mild "endarteritis."

CASE 2.—On Aug. 27, 1939 H. B., a woman aged 73, fell down a flight of stairs and was rendered unconscious for about fifteen minutes. On arousing she was confused and complained of pains in the wrists, knees and head.

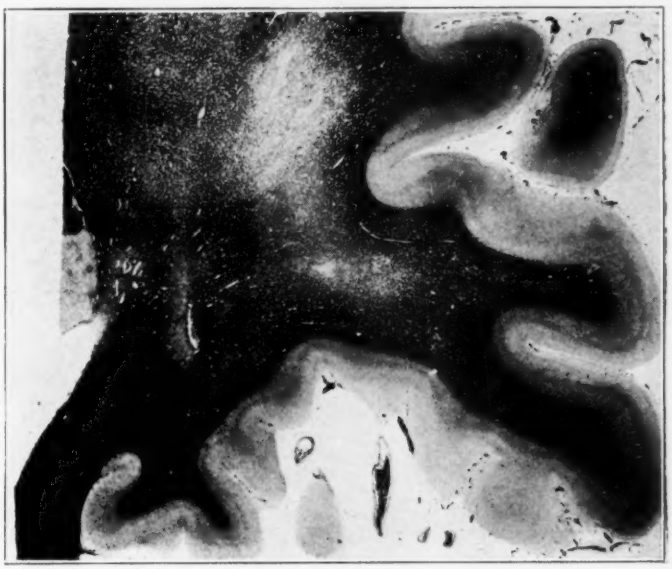

Fig. 5 (case 2).—Cerebrum, showing diffuse demyelination, mainly in the subcortex. Myelin sheath stain; × 4.5.

On admission to the Jewish Hospital her blood pressure was 160 systolic and 92 diastolic, her temperature 97 F., her pulse rate 90 and her respiratory rate 20 a minute. She had a bilateral Colles fracture and lacerations of the right knee. The confusion persisted, but there were no evidences of gross involvement of the central nervous system. The fractures were reduced, without ether anesthesia.

In the hospital vomiting occurred, and she lapsed into semistupor on the second day. Her temperature began to rise and reached 102 F. within two days of her admission; the pulse rate varied from 105 to 125 and the respiratory rate increased to 28 per minute. The spinal fluid was normal and was under pressure of 85 mm. of water. The blood urea was 21 mg. per hundred cubic centimeters. On the fourth day she lapsed into coma.

The blood pressure continued to rise until it reached 194 systolic and 98 diastolic on the fifth day. The temperature continued to rise until it reached 107 F. on the day of death, twelve days after the injury.

The gross observations at autopsy gave no indication of the cause of death.

Microscopic Examination of the Brain.—Myelin sheath preparations showed scattered demyelinated areas of varying size, mainly within the subcortex; some

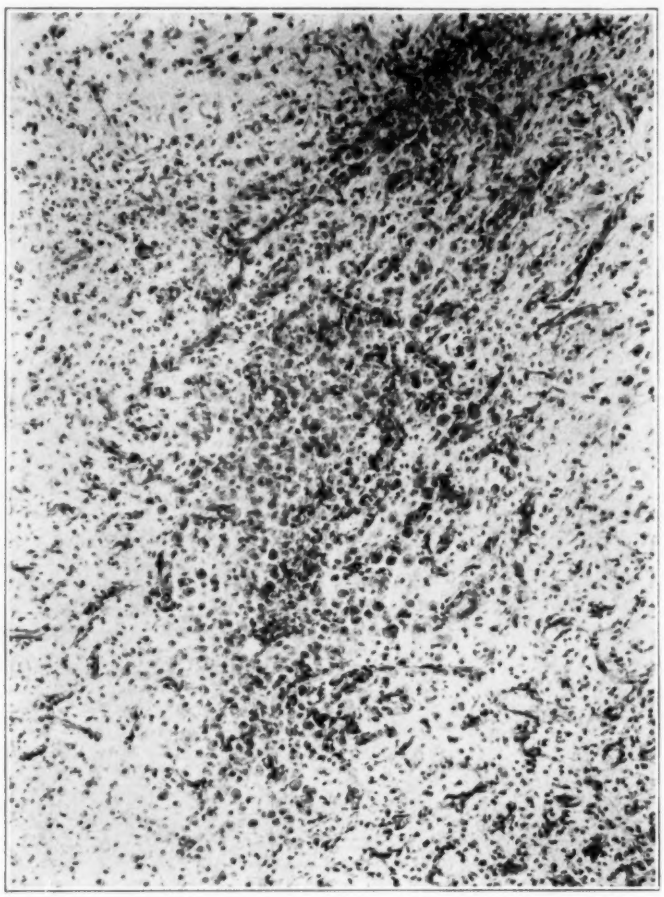

Fig. 6 (case 2).—Cerebrum, showing area of necrosis with accumulation of gitter cells and beginning repair. Toluidine blue stain; × 100.

were small and circumscribed, and others were large and indefinite in outline (fig. 5) because of surrounding areas of status spongiosus. Extensive areas of status spongiosus, without complete loss of fibers, were widely scattered throughout the entire subcortex, in the corpus callosum and, especially, in the frontal lobes. Similar areas were seen in the brain stem, particularly in the pons.

The cell stain (toluidine blue) revealed a dilated subarachnoid space, containing a few phagocytic elements. The demyelinated areas were found to be softenings in various stages. They varied from early tissue coagulation to accumulations of gitter cells (fig. 6) and, finally, areas showing repair by gliosis and vascularization (figs. 7 and 8). The small vessels in both cortex and subcortex, especially the former, showed marked "endarteritic" changes with formation of new vessels.

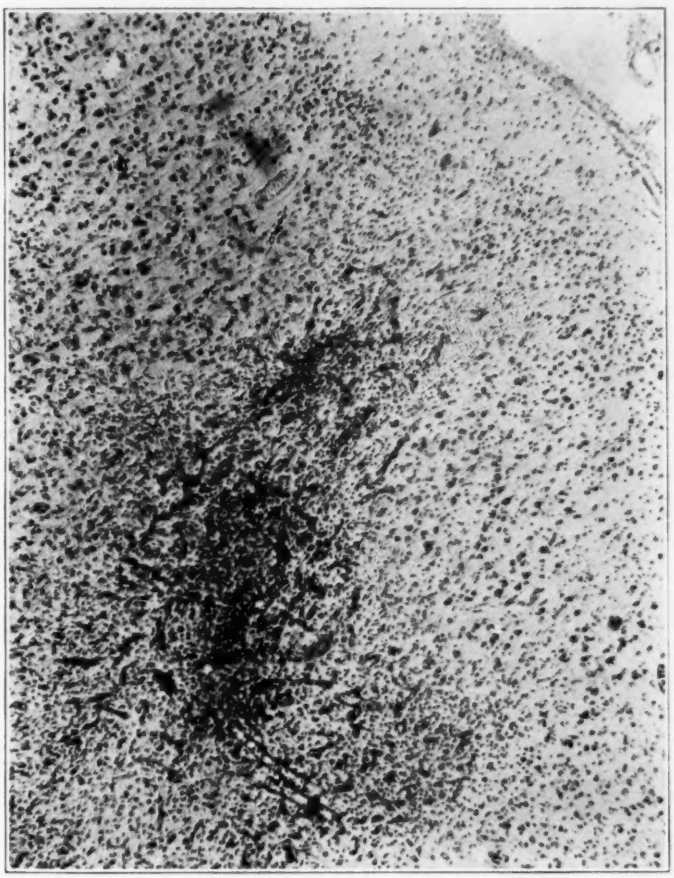

Fig. 7 (case 2).—Cerebral cortex, showing circumscribed area of softening with vascularization and gliosis. Toluidine blue stain; × 700.

The ganglion cells showed universal blanching with abnormal visibility of their processes (cloudy swelling). Occasional groups of sclerotic cells were noted. A universal cell decrease, consistent with the age of 73, was present.

The medium-sized vessels showed thickening and hyalinization of the walls. The larger vessels showed mainly fibrotic changes.

The fat stains showed that many of the small vessels were occluded by globules of fat, frequently in relation to the areas of necrosis but also in areas that appeared normal (fig. 9). The vessels of the cerebellum and brain stem were similarly occluded.

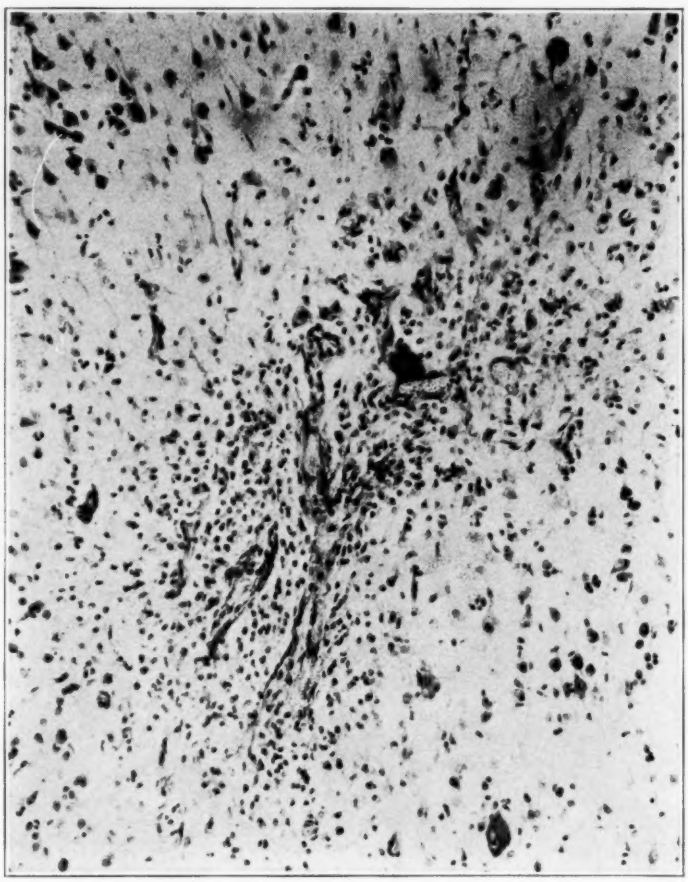

Fig. 8 (case 2).—Cerebral cortex, with a small scar the result of vascular occlusion. Toluidine blue stain; × 240.

COMMENT

Despite the many gross contradictions in the literature on fat embolism, certain facts are established. The most important single etiologic factor is fracture, particularly of the long bones. How and when the fat gets into the circulation is still in doubt. Fat embolism can also occur without fracture, or even without trauma. Its experi-

mental production by etherization alone (Lehman [20]) may give a clue to the mechanism of the process. Lehman questioned the possibility of liberation of sufficient fat to enter the circulation from a fracture at any one point or of the vessels to remain open long enough to suck in sufficient fat for the production of clinical signs and symptoms.

Fig. 9 (case 2).—Subcortex, showing plugging of vessels and areas of necrosis. Fat stain; × 100.

Lehman and McNattin's [33] finding of a high incidence of fat embolism in a routine study of lungs in all types of cases, with or without trauma, may modify one's views on the whole subject. The authors claimed that "the presence of fat embolism in the lung after trauma does not justify the conclusion that such fat has been caused by trauma or that it has caused death."

Histopathologic Changes.—Many authors, especially Lehman, have stressed the occurrence of fat emboli in the lung in nontraumatic conditions. Fat within the vessels of the brain, however, is uncommon except in true fat embolism. With plugging of the small cerebral vessels (even though there are no end arteries in the brain) there result degenerated areas in the brain, the nature of which depends on the rapidity and completeness of occlusion. When slow and progressive occlusion takes place the areas are more likely to be in the nature of coagulation, with gradual cell loss, without accumulations of gitter cells. When the occlusion is rapid and complete there is acute necrosis with outpouring of gitter cells.

The areas of degeneration in our cases were of different ages, especially in case 2, in which the duration of illnes was twelve days. This variation might be interpreted as resulting from periodic projections of fat into the circulation at the point of the original trauma, or it might be attributed to varying difficulties with which the fat works its way through the pulmonary vessels into the greater circulation. The variability of progression in the cerebral vessels is also to be considered.

In the cases in the literature there was involvement of both the cortex and the subcortex, especially the latter, and, as is usual with occlusive vascular lesions in these two areas, different types of involvement were noted. Vance [21] claimed that the gray matter is invaded earliest and most profusely, although Bürger [35] stated that it is only in brains damaged by syphilis or chronic alcoholism that definite lesions of the gray matter can be observed. Two types of lesions have been reported in the subcortex. The first (not found in our second case) is the so-called ring hemorrhage (brain purpura of Schmidt [43]). Considerable difference of opinion exists about the origin of this type of lesion. Some have claimed that rhexis of the vessel wall occurs as a result of pressure from the embolus (Frauendorfer [44]). Others have expressed the belief that it results from extravasation of blood into healthy tissues surrounding an area of necrosis (Gröndahl [19]). Such a lesion consists of a central vessel plugged with fat surrounded by a ring of necrotic tissue, around which is a circular zone of extravasated red blood cells, and is a microscopic hemorrhagic infarct. In older lesions repair is evident, but phagocytic elements containing disintegrated brain and blood elements are still visible; eventually the glial scar becomes dense and the degenerative elements are in the background. The second type of lesion consists of necrotic tissue without hemorrhage

43. Schmidt, O.: Zun Nachweis cerebraler Fett und Luftembolie, Deutsche Ztschr. f. d. ges. gerichtl. Med. **12**:231, 1929.

44. Frauendorfer, O.: Ueber Fettembolie, Beitr. z. gerichtl. Med. **6**:1, 1924.

and is termed a "rarefied area." Such a lesion is usually minute and meshlike and surrounds a blood vessel filled with fat; it is an anemic infarct, in contrast to the hemorrhagic infarct.

Differential Diagnosis of Fat Embolism.—The diagnosis of fat embolism has been one of the most difficult to make in view of the fact that the symptoms are usually atypical and the condition can be confused with so many others, such as shock, cerebral concussion and contusion, cerebral hemorrhage, acute and chronic alcoholism (including delirium tremens), diabetic and uremic coma and bronchopneumonia.

The history of an injury, especially if complicated by fracture of a long bone, may give the first clue to the true nature of the process. A definite "free interval" followed by signs and symptoms of pulmonary and cerebral involvement is characteristic. The condition which most nearly simulates fat embolism in the early stage is epidural hemorrhage, but in the latter pulmonary signs and symptoms are usually absent and there is characteristically a progressive hemiparesis, which gives the clue to the true nature of the condition.

Other signs present at this time which give additional evidence on which a diagnosis of fat embolism can be based include increased pulse rate, pyrexia and involvement of the respiratory apparatus, with cough, respiratory acceleration and signs in the chest that may be confused with bronchopneumonia. The onset of cerebral signs, including irritability, confusion and mental clouding progressing to coma, should rule out a simple pulmonary process and direct attention to the central nervous system.

Prognosis of Fat Embolism.—With the development of the complete cerebral picture the course almost invariably ends fatally. Cases of recovery have, however, been reported (Benestad [42]; Dahl [45]; Nelson [46]). In a study of 89 cases reported by Strauss [38] the mortality was 84.3 per cent. He expressed the belief that even this figure is low because in many of the fatal cases the condition was not recognized. It is probably true that cases of mild fat embolism are much more frequent than is suspected and that the patients recover with few or no sequelae.

SUMMARY AND CONCLUSIONS

Fat embolism must be considered after every trauma, especially if accompanied by fracture of a long bone.

The clinical picture when typical consists of the following stages:

(*a*) A period of shock, which may be absent in an occasional case.

(*b*) A so-called free interval, lasting hours to days, during which there is apparent clearing up of the entire clinical picture. This free interval is supposedly characteristic and diagnostic.

45. Dahl, cited by Groskloss.[9]

46. Nelson, T. Y.: Cerebral Fat Embolism, M. J. Australia **1**:687, 1932.

(*c*) Cardiopulmonary symptoms, consisting mainly of dyspnea, cough with blood-tinged sputum, cyanosis, pulmonary edema and progressive circulatory embarrassment. A diagnosis of bronchopneumonia is usually made at this stage.

(*d*) Cerebral symptoms, consisting of restlessness, anxiety, confusion, hallucinations and focal and generalized convulsions. These symptoms resemble delirium tremens, with which they have been confused.

(*e*) A terminal picture, consisting of increasing temperature, which may reach as high as 108 F., cutaneous petechiae, stupor, gradually increasing to coma and death. Of diagnostic importance is the presence of free fat in both sputum and urine.

Mild disturbances following trauma with pulmonary and cerebral symptoms that are vague and indistinct have been attributed to fat embolism. Recovery in cases of this type is the rule.

Alcoholism apparently predisposes to the development of fat embolism. Inhalations of ether or chloroform increase the possibility of fat embolism following trauma. Many authors have warned against giving ether and chloroform in any case of trauma.

The changes within the central nervous system result from the plugging of the blood vessels by fat emboli. Within the gray matter anemic infarcts are the usual lesions, while within the white matter hemorrhagic infarcts are more common. Unless death follows quickly the lesions are of different ages. They explain the progressive cerebral picture.

Treatment of the well established condition has hitherto been unsatisfactory. Only one recent report in the literature (Rappert [27]) expresses optimism. Prophylactic measures which have been suggested include ligation of veins and lymphatics from the injured area. The occurrence of fat embolism after ligation of both veins and lymphatics has given credence to Lehman's idea that fat embolism is not the result of invasion of the blood stream by fat at the point of fracture but that some chemical is released which causes a coalescence into large visible masses of the microscopic globules of fat that are normally present in the blood.

VASOSPASM AND FOCAL CEREBRAL ISCHEMIA

AN EXPERIMENTAL STUDY

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The present article deals with the vasoconstrictions that can be produced in the pial arterial vessels of animals by electrical and mechanical stimulation. The purpose of the investigation was mainly to determine, if possible, a method of producing temporary focal cerebral ischemia.

Since the middle of the last century many observers have suggested that such ischemia might be the causative factor in epilepsy, migraine, temporary hemiplegias, hypesthesias, aphasias and other transitory neurologic phenomena. No one, however, as far as I know, has produced and studied the effect on the brain of temporary focal cerebral ischemia.

In this paper a method is described whereby temporary focal cerebral ischemia may be produced. Such ischemia did not cause any clinical epileptiform manifestations in unanesthetized cats so long as the motor gyrus was not involved in the ischemia. That subclinical epileptiform neuronal activity might have occurred as a result of the ischemia cannot be ruled out in this investigation but might be determined by using the electroencephalographic method during the period of ischemia.

In the investigation evidence was found which seems to prove that stretch of a vessel wall is an adequate stimulus to produce constriction. The significance of this, as well as of a number of other observations made during the course of the investigation, is discussed.

TECHNIC

The experiments were carried out on 30 cats, 1 dog and 4 monkeys. The animals were anesthetized by the drop ether method or by intraperitoneal injection of dial, 0.5 cc. of a 10 per cent solution per kilogram of body weight being given.

A large decompressive craniotomy was performed in each case. At times this was done at first on one side and a few hours later on the other. On opening the dura a Petri dish was immediately laid over the cranial defect and gauze soaked in Ringer's solution closely applied to the edges of the dish to prevent the entrance of room air and drying of the cortex. In the center of the Petri

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dish was a small hole through which a glass stimulating rod or electrodes could be inserted. A microscope was then mounted over the cortex and the vessels observed, either with or without the presence of the Petri dish.

For electrical stimulation of the pial blood vessels a thyratron was used. This was constructed by André Cipriani in this laboratory and is similar to that described by Schmitt and Schmitt [1] in 1932. Both unipolar and bipolar electrodes were employed at different times. These were made of platinum and fixed in a glass holder. The wave frequency used for stimulation varied between 55 to 65 per second, and the intensity of the current was in most cases not greater than that usually used for stimulation of the human cortex at operation. A stimulus which was just great enough to produce motor movement when applied to the sigmoid gyrus (motor cortex) of the unanesthetized cat was usually of sufficient intensity to cause marked constriction of a pial vessel. The range of voltages employed was not accurately determined.

OBSERVATIONS

Effect of Mechanical Stimulation on Individual Pial Blood Vessels in the Cat.—Preliminary observations on 6 cats confirmed the observations of Florey [2] (1925) that mechanical stimulation of a pial arterial vessel will cause it to constrict.

It was found that gentle or heavy stroking of arterial vessels of all sizes with the tip of a glass rod produced vasoconstriction (figs. 1 and 2). It was usually necessary to stroke the vessel at right angles to its long axis. By this means the vessel wall could be stretched, and stretch itself appeared to be an adequate stimulus to produce constriction. The contraction usually occurred only over the area of vessel stimulated and was never propagated for long distances, as has been described in mesenteric vessels by Chase.[3] However, constriction frequently occurred for a short distance on either side of the area in contact with the stimulus. It was felt that this was due to the fact that the maximum stimulation had been applied at the site of contact of the stimulus but that the vessel was stretched (and hence stimulated) over a wider area. This phenomenon was well demonstrated in the following manner:

A very fine thread was passed beneath a small pial artery and the diameter of the artery measured microscopically at a distance of about 2 mm. from the point of contact of the thread. Traction was now applied for a few seconds to

1. Schmitt, O. H. A., and Schmitt, F. O.: A Universal Precision Stimulator, Science **76**:328, 1932.

2. Florey, H. W.: Microscopical Observations on the Circulation of the Blood in the Cerebral Cortex, Brain **48**:43, 1925.

3. Chase, W. H.: (*a*) Anatomical and Experimental Observations on Air Embolism, Surg., Gynec. & Obst. **59**:569, 1934; (*b*) Cerebral Thrombosis, Hemorrhage and Embolism: Pathological Principles, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:365, 1938.

the thread so that the vessel was stretched. Traction on the thread was then released and a second reading of the vessel diameter taken at the same point as before.

In many such experiments it was found that stretching the vessel in this manner frequenty caused it to constrict to obliteration at the point of contact of the thread and to approximately 50 per cent of its normal diameter at a distance 2 mm. away from the thread. The whole portion of vessel constricted at times showed some degree of "beading" of its wall. Such experiments seem to justify the conclusion that stretch of the wall of a pial artery will cause it to constrict.

Gentle stimulation of a pial artery with a glass rod frequently produced complete obliteration of the lumen of the vessel, and the movement of the corpuscles in branches of the main trunk leading into the

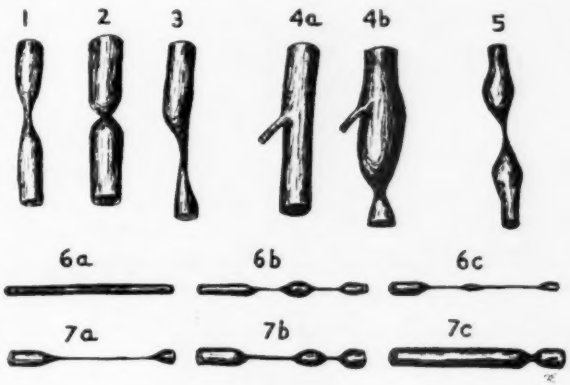

Fig. 1.—Drawings *1* to *5* were taken from photomicrographs of the cat's pial vessels constricted by mechanical stimulation. The localized nature of the constrictions, as well as other features mentioned in the text, is well illustrated.

Drawings *6a* to *6c* represent the development of constrictions following stimulation of a vessel with bipolar electrodes leading to a thyratron (intensity 5). One and a quarter minutes elapsed between the time of stimulation (*6a*) and the degree of constriction present in *6c*.

Drawings *7a* to 7c show the redilatation of a vessel after it had been constricted by running the electrodes along several millimeters of its length. Ten minutes elapsed while the vessel changed in caliber from that shown in *7a* to that shown in *7c* (intensity 5 on the thyratron dial).

constricted area ceased as far back as the first collaterals. At other times stronger stimulation, such as forcefully stretching the vessel from side to side with the tip of the rod, was required to bring on the constriction. This was occasionally true in one portion of a vessel, whereas on either side of this area in the same vessel lighter stimulation caused a very localized constriction. Some vessels were completely refractory

to stimulation or became so after a period of constriction. Occasionally on gentle stretching of a vessel, dilatation rather than constriction resulted. However, despite the variability in sensitivity of various vessels

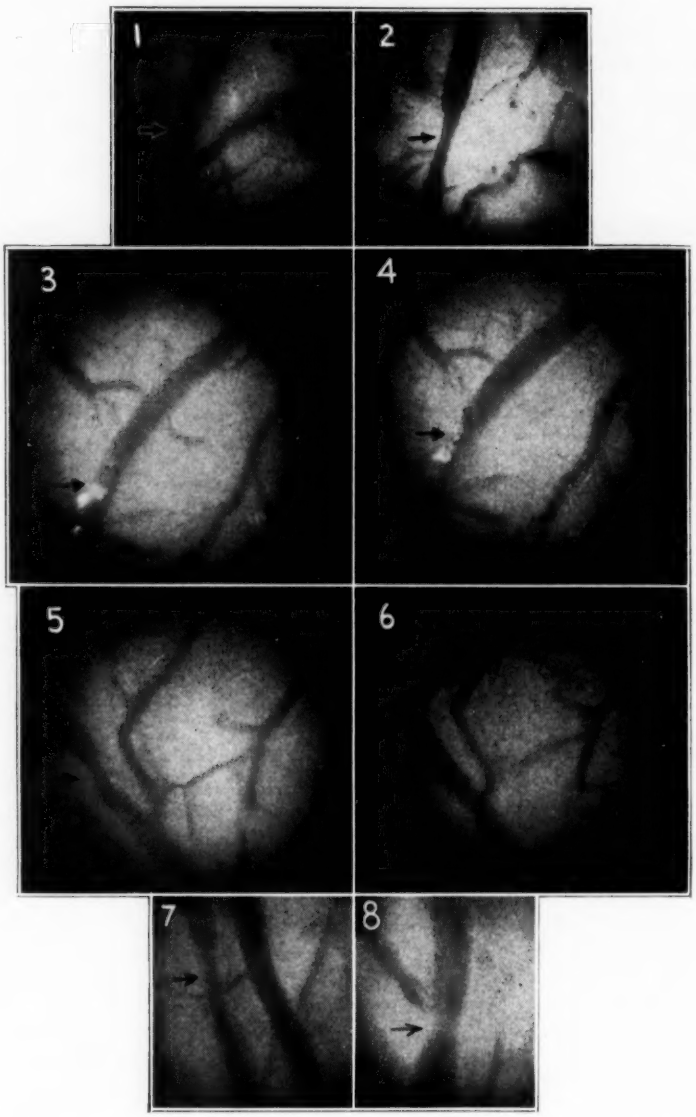

Fig. 2.—Photomicrographs of a cat's pial vessels. *1* and *3* show normal vessels; *2* and *4*, the same vessels after they have been constricted by mechanical stimulation with the tip of a glass rod; *5*, a pial vessel constricted by mechanical stimulation; *6*, the same vessel five minutes later, and *7* and *8*, constrictions in pial vessels following mechanical stimulation.

to stimulation, the majority contracted promptly when the cortex was first exposed and continued to do so on stimulation over a period of hours if the brain was protected with a glass covering.

The duration of the spasms was also variable, ranging from several seconds to twelve minutes, depending on the sensitivity of the vessel and on the duration and strength of the stimulus. In a fresh cortex the average duration of a vessel spasm produced by rather vigorous stretching (stroking) was about three minutes. The time for the constriction to reach its maximum varied from a few seconds to nearly a minute after stimulation.

It has frequently been observed that dilatation occurred on either side of an area of constriction. This dilatation at times did not attain its maximum until an interval of one-half to two minutes had elapsed.

If several millimeters or more of a vessel was constricted by mechanical stimulation, redilatation was usually not uniform but occurred in a bologna sausage fashion—areas of annular constriction alternating with areas of dilatation. When dilatation was complete there was at times a reactive hyperemia, the vessel being increased in size by as much as one-third its normal diameter.

The aforementioned observations apply to arterial vessels of all sizes. The venous capillaries did not show any direct reaction to stimulation, however, and the larger arterial branches, such as the middle cerebral, were somewhat more refractory than the medium-sized and smaller vessels. The basilar artery, on the other hand, constricted promptly to almost complete obliteration when stimulated in the usual manner with a blunt rod. The latter observation was made on 10 cats, in which the basilar artery was exposed through a burr hole in the base of the skull (during experiments for a different purpose).

The following interesting observation was made, which is difficult to explain: If, as stated, the cortex was covered with a Petri dish immediately after the dura had been opened, most pial vessels were found to constrict on mechanical stimulation over a period of hours. However, if the cortex was left exposed to dry air for a short time, almost all the vessels frequently became refractory to mechanical (or electrical) stimulation. On the other hand, in many experiments, after several hours of exposure to air the vessels again constricted as promptly as, if not more so than, those in the fresh brain. This was true even after exposure to room air for nine hours, the brain having been irrigated from time to time with cool or warm Ringer's solution. These results suggest that there are three stages in the excitability of the vessels to mechanical stimulation (and the same has been found to be true of electrical stimulation): an initial stage, in which the cortex and its vessels are in approximately the normal state; a second, in which the vessels are refractory to stimulation, owing perhaps to exposure, trauma during

craniotomy or the effect of irrigation with Ringer's solution or the temperature of the solution, and a third, in which the pial vessels are again irritable, despite changes in temperature and exposure.

Effect of Electrical Stimulation on Individual Pial Vessels in the Cat.—As with mechanical stimulation, it was found that arteries

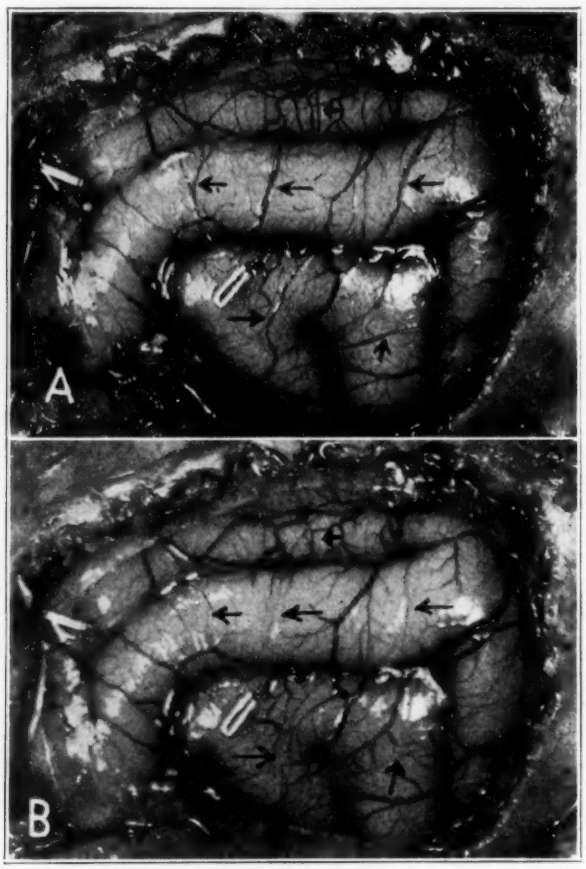

Fig. 3.—Photographs of a cat's brain (*A*) before and (*B*) immediately after the pial vessels had been constricted by electrical stimulation. Note that the majority of the arteries visible in *A* are no longer visible in *B* or are seen as faint gray lines, as indicated by the arrows. The vessels still plainly visible are chiefly veins. Bipolar electrodes and a thyratron were used for stimulation (intensity 5). The vessels were constricted by gently moving the electrodes over all visible vessels.

arterioles and capillaries (not venous capillaries) constricted promptly on electrical stimulation (fig. 3). With a weak unipolar stimulus it could be shown that the constriction was largely localized to the site

of stimulation and was propagated for only a short distance, if at all, in either direction. Such propagation as there was probably resulted from spread of the electric current. A very weak stimulus was usually sufficient to cause complete obliteration of the vessel lumen, but the degree of contraction varied with both the duration and the strength of the stimulus.

In a fresh cortex protected from air, pial vessels usually constricted to obliteration on less than one second's stimulation with the thyratron dial at 2 to 3, which is usually below the threshold stimulus required to produce motor movement from the unanesthetized cat's cortex (the threshold stimulus was usually 3 to 5 on the intensity dial).

With the thyratron set at 5 (and using a bipolar electrode) a single stimulation of less than one second produced spasm at each electrode, which advanced gradually to involve the portion of vessel lying between the electrodes. The maximum contraction of the vessel wall was frequently not reached until one and one-half minutes after stimulation. The vessel did not always contract uniformly, and at times the whole area which had come under the influence of the stimulus showed beading, constrictions alternating with normal or slightly dilated portions. Most of the dilated portions gradually gave way to constriction, but only after a latency of as long as one and one-half minutes. The duration of the constriction varied considerably with the same stimulus. With the thyratron at 5 a stimulus applied for two seconds to a pial vessel, recently exposed, produced a contraction lasting on an average three to five minutes. However, contractions of much longer duration, up to several hours, sometimes occurred, but these usually followed only stimulation of greater duration and strength. Even after such prolonged constriction the blood flow through the vessel appeared to be restored in normal fashion when it again dilated.

Effect of Electrical and Mechanical Stimulation on the Pial Vessels of Dogs and Monkeys.—With mechanical or electrical stimulation, it was found that the pial vessels in dogs (anesthetized with dial, 0.5 cc. of a 10 per cent solution per kilogram being given intraperitoneally) showed the same type of spasms as those described in the cat. However, with mechanical irritation the stimulus had to be more forceful to produce obliteration of the vessel lumen and the vessels showed more tendency to become refractory than was the case in cats. The same was true of electrical stimulation, when a current of greater strength was often necessary to produce constriction of the vessel.

Experiments were also performed on 2 monkeys. In these animals the cortex had been exposed to air for some time before stimulation was carried out, and in both of them the vessels failed to constrict. With a monkey under dial anesthesia, a craniotomy was then performed and

the cortex covered with a Petri dish immediately on opening the dura. The pial vessels in this animal also failed to contract on mechanical or electrical stimulation, with the exception of one vessel, which showed a feeble spasm. A similar experiment was then done on a monkey, with the use of local and light ether anesthesia. When the animal had recovered from the ether anesthesia it was found that the vessels contracted on electrical stimulation. Repeated stimulation, however, was usually necessary to bring about spasm. However, after a vessel had once been partially constricted it became more sensitive for a time, and it was then possible by repeated stimulation to keep most vessels over an area of cortex constricted at the same time.

It is concluded from these experiments that the dog's pial vessels are somewhat less sensitive to mechanical and electrical stimulation than are the cat's and that the monkey's pial vessels are more refractory to direct stimulation than the dog's.

Effect of Certain Drugs on Constricted Pial Vessels.—In 3 experiments (on cats) the effect of acetylcholine on the constrictions described was studied. To do this two vessels were observed microscopically. One was constricted to obliteration by electrical stimulation; the other was not stimulated and remained normal. Acetylcholine, 0.2 mg. per kilogram of body weight, was then injected intravenously. The normal vessel dilated promptly, but the vessel which had been constricted by electrical stimulation was apparently not affected by the acetylcholine. This observation was repeated a number of times on different vessels, with the same result, except that the constricted area in some vessels appeared to relax slightly more rapidly after the injection of the acetylcholine than is normally the case when no acetylcholine is used.

Inhalation of amyl nitrate for ten seconds likewise appeared to have little or no effect in dilating constricted vessels, although it caused prompt dilatation of neighboring normal vessels. Inhalation of carbon dioxide also had no apparent effect on constricted vessels.

Combined Electrical Stimulation of Pial Blood Vessels and of the Cervical Portion of the Sympathetic Trunk.—In 1 cat a pial blood vessel was stimulated with the thyratron at 4 for two seconds, and microscopic readings were taken during the period of its constriction and redilatation. The procedure was then repeated, but at the same time the sympathetic nerve trunk in the neck on the same side was stimulated constantly with electrodes leading from an induction coil. This experiment was carried out on a number of vessels, and it was found that the time for the vessel to reach its maximum constriction and to redilate was approximately the same with and without concurrent stimulation of the cervical portion of the sympathetic trunk.

A Method of Producing Temporary Focal Cerebral Ischemia.—As is well known, in the opinion of many it has seemed possible that a local vascular spasm, or, more correctly, focal cerebral ischemia, might initiate a convulsion and that repeated local vascular spasms may in some cases be part of the mechanism responsible for epilepsy (Cobb [4]; Kennedy and associates [5]).

With the technic of direct stimulation of pial vessels it appeared that a method might be developed for testing this theory, or at least for studying it. Until the present no adequate way has been reported for producing experimental temporary focal cerebral ischemia. Constrictions in a single pial vessel (like those described in the preceding pages) do not, of course, give rise to ischemia because of the rich vascular anastomosis which is present (Pfeifer [6]; Cobb [7]). However, if all pial vessels could be constricted at the same time over an area of cortex it seemed that ischemia of the underlying brain would result.

A number of experiments were therefore carried out in the hope of producing such ischemia. As will be seen, it was found possible by direct stimulation to constrict most of the arteries, arterioles and capillaries over a given area of cortex and by this means to cause temporary ischemia of the underlying brain.

Effect on Cortical Blood Flow of Focal Vascular Spasm.—In 3 experiments (on cats) two thermocouples leading to a thermoelectric blood flow recorder were inserted diagonally about 2 mm. into the cerebral cortex, one in the posterior sigmoid gyrus (thermocouple 1) and one in the suprasylvian gyrus (thermocouple 2). The sensitivity of the preparation was then tested by injecting 0.25 cc. of a 1:10,000 solution epinephrine hydrochloride into the femoral vein and recording the effect on the blood flow. (During this period the cortex was protected in the usual manner with a Petri dish, as already described.) The vessels about thermocouple 2 and those leading to this area were now stimulated electrically with the thyratron at 3 to 7 (the threshold for movement from the motor cortex in cats recovered from ether anesthesia is about

4. Cobb, S.: Cerebral Circulation: A Critical Discussion of the Symposium, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:719, 1938.

5. Kennedy, F.; Wortis, B., and Wortis, H.: The Clinical Evidence for Cerebral Vasomotor Changes, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**: 670, 1938.

6. Pfeifer, R. A.: Die Angioarchitektonik der Grosshirnrinde, Berlin, Julius Springer, 1928; Grundlegende Untersuchungen für die Angioarchitektonik des menschlichen Gehirns, ibid., 1930.

7. Cobb, S.: The Cerebral Circulation: XII. The Question of End Arteries of the Brain and Mechanism of Infarction, Arch. Neurol. & Psychiat. **25**:273 (Feb.) 1931.

3 to 5). At the beginning of stimulation there was frequently a rise in blood flow at thermocouple 2, but as the vessels stimulated showed constriction there was usually a marked fall in blood flow without any significant change in blood pressure, or in blood flow at thermocouple 1 (fig. 4). As the vessels redilated the blood flow again increased. These changes were obtained at times when vessels several millimeters to 1.5 cm. away from the thermocouple were stimulated, an indication that the results were not due to an increase in heat of the cortex from the

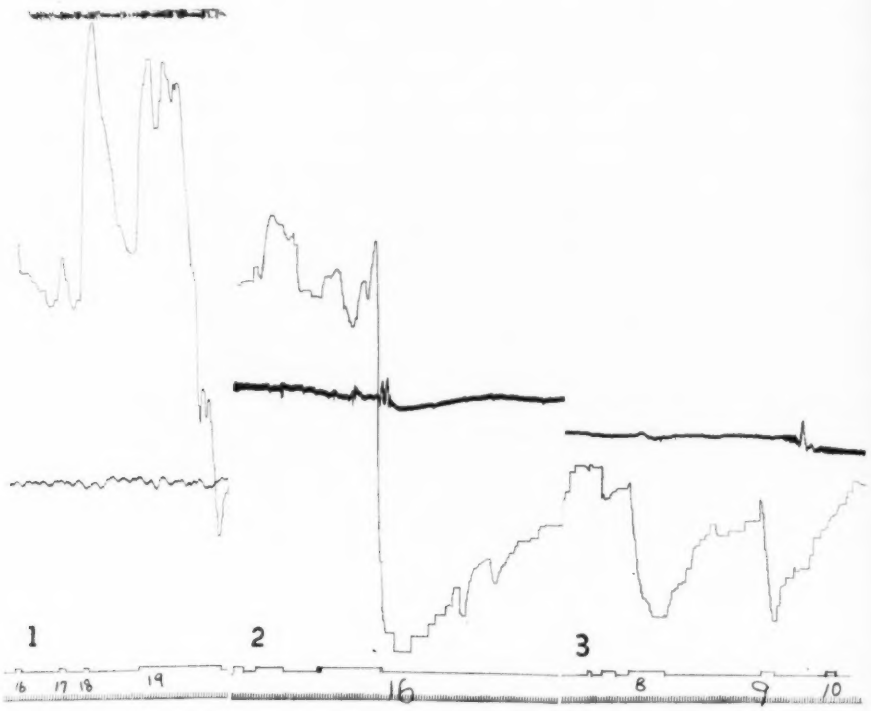

Fig. 4.—Tracings *1* to *3* show the effect on the blood flow in the cortex of constricting, by electrical stimulation, blood vessels supplying an area of gray matter in which a thermocouple (leading to a thermoelectric blood flow recorder) has been inserted. Note that in each case when stimulation is first started there is a rise in blood flow, followed by a rapid and marked fall. In tracings *1, 2* and *3* the periods of stimulation are shown by numbers: *19* in tracing 1, *16* in tracing *2* and at *8* and *9* in tracing *3*.

electrical stimulation. From these experiments it was obvious that vasoconstriction brought about in this way gave rise to a markedly diminished blood flow in the underlying cortex, if not to complete ischemia.

Demonstration of Focal Cerebral Ischemia by Means of Intravital Staining.—A large bilateral craniotomy was performed on a cat. The vessels over one suprasylvian gyrus and those immediately surrounding it were then stimulated with bipolar electrodes leading to a thyratron. The intensity of stimulation varied from 6 to 8 as indicated on the thyratron dial. It was found that by gently stroking the vessels with the electrodes all visible pial arteries, arterioles and capillaries could be kept in spasm for periods up to half an hour or more. When stimulation ceased the vessels dilated in the usual manner, many showing a bologna-sausage type of constriction and dilatation.

During the period of stimulation in which constriction of the vessels appeared complete, 60 cc. of a 1 per cent aqueous solution of gentian

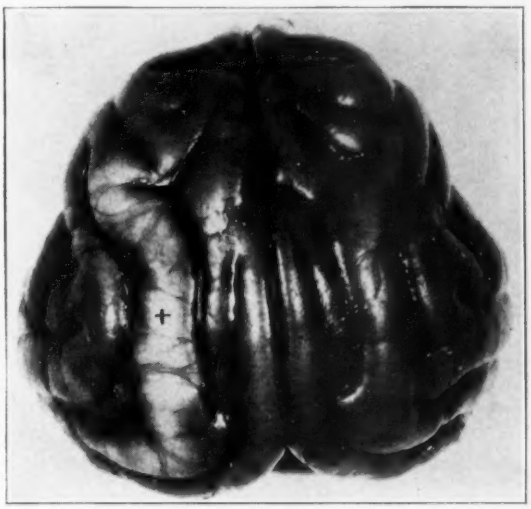

Fig. 5.—This photograph was taken one hour after the termination of an experiment in which the arteries, arterioles and capillaries were constricted over the left suprasylvian gyrus (marked +) by electrical stimulation. During the period of constriction 60 cc. of a 1 per cent solution of gentian violet was injected into the femoral vein. The whole brain, except for the left suprasylvian gyrus, turned deep blue. The gyrus stimulated remained whitish pink, showing that it had been rendered ischemic by the stimulation (see text).

violet was injected into the femoral vein by an assistant. The brain rapidly turned a deep blue except in the area where the blood vessels had been constricted. This area remained white. At the same time the cat continued to breathe actively and the heart, although rapid in rate, beat forcefully. The animal was then killed by injection of dilute solution of formaldehyde U. S. P. (1:10) into the femoral vein and by a stab wound in the heart. The brain was removed promptly and photographed about one hour later (figs. 5 and 6). This experiment

was repeated on 3 cats, with the same result. Coronal sections of the brains showed that ischemia had been almost complete through the entire depth of the cortex in a large portion of the area stimulated. It is interesting that the zone of ischemia was frequently triangular, or wedge shaped, as shown in figure 7. The triangular shape of the ischemic area is explained by the anatomic distribution of the perforating vessels from the pia. Results similar to those just reported were obtained in

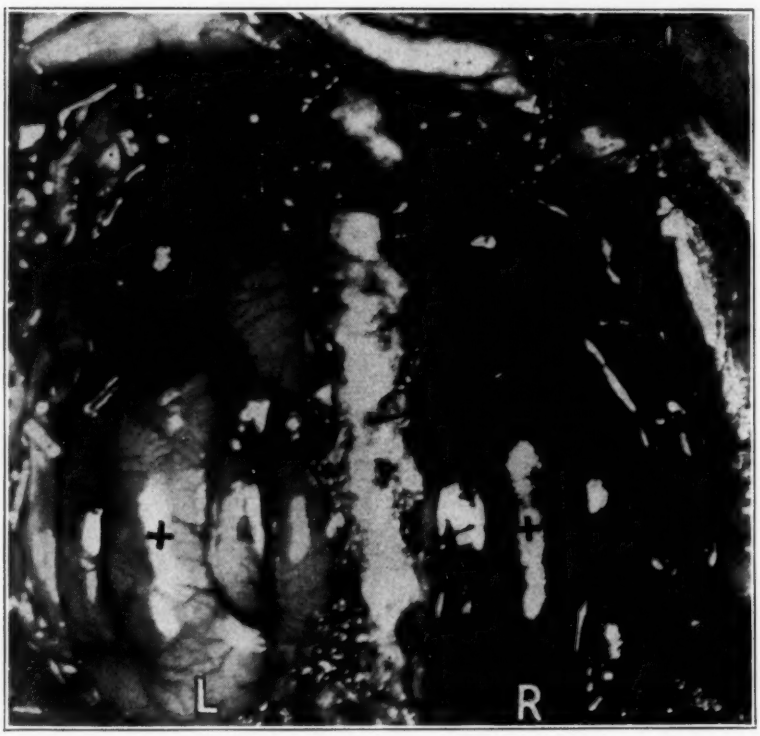

Fig. 6.—The experiment in this case was identical with that described in figure 5 except that the arterial vessels were constricted over the whole left cerebral hemisphere. The photograph shows that the gentian violet injected into the femoral vein turned the right cerebral hemisphere blue, whereas the left hemisphere, over which the vessels were constricted by electrical stimulation, remained whitish pink.

2 cats by substituting chlorazol sky blue (10 cc. of a 14 per cent aqueous solution) for gentian violet.

Effect of Temporary Focal Cerebral Ischemia on Cats Recovered from Ether Anesthesia.—To study the immediate physiologic effect of temporary focal cerebral ischemia, 5 experiments were carried out on cats recovered from ether anesthesia.

With the same technic of electrical stimulation as that described in the preceding section, small and large areas of cortical ischemia were produced in the temporal, parietal or occipital region of each of 5 cats after they had recovered from the effects of ether anesthesia. This treatment had no apparent clinical effect on the animals. No motor movements or other epileptiform manifestations were observed. Whether subclinical epileptiform neuronal activity occurred could not be determined by these experiments.

In the experiments the effect of producing cortical ischemia of the motor gyrus could not be properly evaluated, as the electrical stimulation itself frequently had a direct effect on the motor nerve cells.

Focal Cerebral Ischemia Produced by Mechanical Stimulation of Pial Vessels.—Like electrical stimulation, mechanical stimulation can produce complete constriction of pial vessels over wide areas of cortex, and over

Fig. 7.—Photograph of the brain shown in figure 5. The arrow points to the patch of ischemia in the suprasylvian gyrus. Note that this patch is in the form of a definite triangle.

small areas all arterial vessels can be kept constricted at the same time for periods as long as half an hour. When stimulation is stopped dilatation of most vessels is usually complete in three to five minutes.

Experiments were carried out with this type of stimulation on 3 cats in a manner similar to that described with electrical stimulation. Thus, diminished blood flow in the cortex was demonstrated with the blood flow recorder after mechanical stimulation of vessels surrounding the thermocouple, and small patches of ischemia were shown to be present in the cortex (after mechanical constriction of vessels) on intravital injection of gentian violet. However, the degree of diminished blood flow and the areas of ischemia were less marked and more difficult to produce than when the vessels were constricted electrically. Constriction of pial vessels in this manner, even over large areas, including the sigmoid (motor) gyrus, had no apparent immediate clinical effect on cats recovered from ether anesthesia.

During the course of the present investigation several other observations were made that are worthy of note.

Effect on the Cortex of Strong Electrical Stimulation.—In 2 cats a gyrus (in 1 case the sigmoid and in 1 the suprasylvian) was stimulated for twenty minutes with the thyratron at 9. A stimulus of this intensity is close to the maximum for the thyratron and is about twice the threshold stimulus required for movement from the sigmoid gyrus. The stimulus was applied repeatedly for two seconds at two to three second intervals for twenty minutes. In this manner the whole gyrus was systematically covered, the greater number of the stimuli being applied directly to the visible arterial vessels.

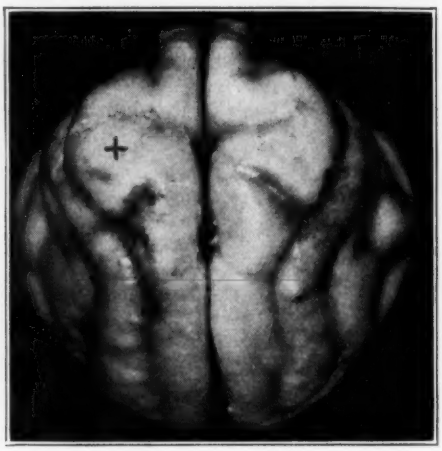

Fig. 8.—Photograph of a cat brain, the sigmoid gyrus and cortex immediately adjacent to which had been stimulated electrically for half an hour. Note that there is swelling of the left sigmoid gyrus, marked + (see text).

In both cats, about fifteen minutes after the onset of stimulation it was noted that there was marked swelling of the gyrus stimulated. This swelling was present when the gyrus was very pale from vasoconstriction of all visible arterial vessels. The swelling, therefore, could not have been due to increased blood flow through the gyrus. It became even more marked when the blood supply returned to the gyrus. In 1 cat the swelling was still very evident at autopsy, forty-eight hours later. This had partly disappeared after fixation for twenty-four hours in solution of formaldehyde, when the photograph was taken (fig. 8). The other cat was not killed for fifteen days after operation, and the swelling by this time had been replaced by definite atrophy of the stimulated gyrus. (The histologic changes following this type of stimulation will be reported at a later date.)

Effect on the Pial Vessels of Passing 110 Volts Through the Brain.—In 4 cats electrodes were placed, one on the upper lip and one in the temporal muscle overlying a cerebral hemisphere (bilateral craniotomy having been performed). The electrodes led to a plug which was connected to the 110 volt main. The alternating current was then passed through the brain for one to three seconds by closing the circuit. The pial arterial vessels immediately became obliterated by constriction and for a few seconds were invisible to the eye (fig. 9). Most of the veins also diminished in diameter, but this may have been due to lessened arterial flow. At times pial arteries remained constricted for as long as three minutes. Constrictions from stimulation with 110 volts, however, were never as prolonged as they are with stimulation from an induction coil or a thyratron. The vessels in the hemisphere directly

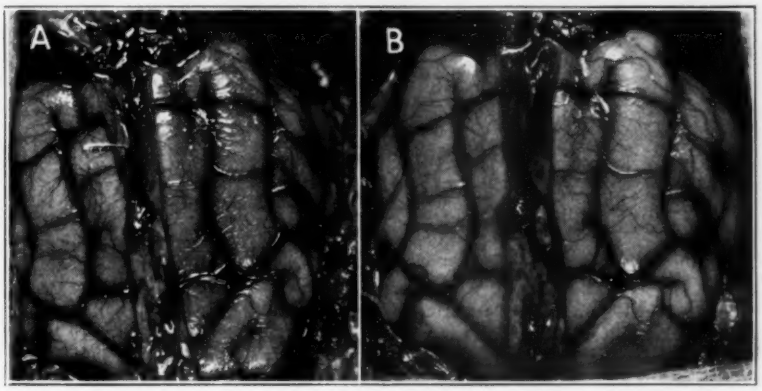

Fig. 9.—Photographs of a cat's brain, (*A*) in its normal state and (*B*) approximately three seconds after a current of 110 volts had been passed through it for three seconds. Note that after stimulation many of the arteries and veins show some degree of constriction. For the technic used in stimulation see the text.

between the electrodes showed more constriction than those in the opposite hemisphere. This type of stimulation, incidentally, produces a violent tonic and clonic convulsive seizure in both cats and rabbits. Similar observations have been made previously. For instance, Morrison, Weeks and Cobb,[8] in an investigation of the histopathologic changes which follow different types of electric shock in mammalian brains, observed that on stimulating with an alternating current the intracranial arteries contracted during the shock and for a short time after the cessation of electrical stimulation.

8. Morrison, R.; Weeks, A., and Cobb, S.: Histopathology of Different Types of Electric Shock on Mammalian Brains, J. Indust. Hyg. **12**:364, 1930.

COMMENT

The effect of direct stimulation on pial vessels was apparently first observed by Schultz [9] in 1866, who found that these vessels constricted on electrical stimulation. Apart from his work, little interest was taken in this particular problem until Florey's paper appeared in 1925. This author reported in detail how spasms could be produced in individual pial vessels by direct mechanical and electrical stimulation. His work was confirmed by Riser, Meriel and Planques.[10] In the present investigation Florey's observations have again been confirmed and extended and his results used to develop a method of producing temporary focal cerebral ischemia. In the discussion to follow certain physiologic aspects of pial vessel spasm will be mentioned before going on to a consideration of cerebral ischemia.

It has been shown in this investigation that a stimulus apparently adequate to produce vasoconstriction of a pial arterial vessel is stretch of the vessel wall, such as is produced by rolling it from side to side or stretching it by means of a silk thread looped about the vessel. This is an important point, for if such stretching of the vessel wall will produce constriction, then endovascular pressure (or stretch) should also cause a degree of vasoconstriction. On the basis of this simple observation alone, therefore, one might postulate that the pial vessels (in the cat) are capable of maintaining their tone, at least in part, by a purely local mechanism.

Forbes, Nason and Wortman [11] considered such a hypothesis on the basis of experiments showing that "when the pressure falls to a level that is critical for the individual animal (usually 60 mm. of mercury) the arteries dilate. Conversely, when the pressure rises the dilated arteries constrict and soon regain their normal caliber." They supported their observation by referring to Bayliss,[12] who suggested that relaxation of arterioles in response to a fall in blood pressure, as well as contraction in response to increased tension, might be explained as a characteristic of smooth muscle, for the latter is known to react in a similar manner in other organs. It is, in fact, well known that smooth muscle in general "is caused to enter into contraction by stretching" (Bayliss [12]).

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9. Schultz, A.: Zur Lehre von der Blutbewegung im Innern des Schädels, St. Petersburg. med. Ztschr. **11**:122, 1866.

10. Riser, M.; Meriel, P., and Planques: Les spasmes vasculaires en neurologie. Etude clinique et expérimentale, Encéphale **26**:501, 1931.

11. Forbes, H. S.; Nason, G. I., and Wortman, R. C.: Cerebral Circulation: XLIV. Vasodilation in the Pia Following Stimulation of the Vagus Aortic and Carotid Sinus Nerves, Arch. Neurol. & Psychiat. **37**:334 (Feb.) 1937.

12. Bayliss, W. M.: The Vasomotor System, London, Longmans, Green & Company, 1923, p. 14.

Fog likewise demonstrated, in experiments on cats, that a decrease of blood pressure was followed by dilatation of the pial arteries [13] and that, conversely,[14] an increase of arterial pressure caused constriction of these vessels. He also showed [15] that these pial vascular responses were identical whether the sinus and the aortic nerves, the cervical portion of the sympathetic trunk and the vagus nerves were intact or severed. He concluded: [15]

> The reactions of the pial arteries resulting from change of the endovascular pressure indicate the presence of a vasomotor regulatory mechanism within the limits of the cerebral vascular tree. This mechanism assists in keeping the blood flow to the brain constant during various physiological and pathological conditions of the general circulation.
>
> . . . It is suggested that it [the specific mechanism] depends on properties inherent in the smooth muscles of the arterial wall.

Some interesting observations that might be explained on the basis of the aforementioned hypothesis are those described by Villaret and Cachera.[16] These authors found that air emboli injected into the pial vessels were not a sufficiently intense stimulus to cause vasoconstriction. However, on injecting solid emboli, such as ground-up pumice stone, they obtained marked constrictions. The difference in the effect of these emboli may well be due to the fact that an air embolus can be compressed into a very thin column which might not cause much stretch of the vessel wall, whereas with a solid embolus, like pumice stone, a particle larger than the normal diameter of the vessel would stretch it, and constriction would probably result from the stretch.

In 1925 Florey noted that the constrictions in pial vessels resulting from mechanical or electrical stimulation were localized to the site of the stimulus and were not propagated. This fact has been confirmed in the present investigation, except that, as mentioned, a vessel will constrict for some distance on either side of the area in contact with the stimulating agent when this produces stretch of the vessel wall. This localization of the constriction to the site of the stimulus has been observed by Lewis,[17] Krogh [18] and many others who have studied the

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13. Fog, M.: Cerebral Circulation: I. Reaction of Pial Arteries to Fall in Blood Pressure, Arch. Neurol. & Psychiat. **37**:351 (Feb.) 1937.

14. Fog, M.: Cerebral Circulation: II. Reaction of Pial Arteries to Increase in Blood Pressure, Arch. Neurol. & Psychiat. **41**:260 (Feb.) 1939.

15 Fog, M.: The Relationship Between the Blood Pressure and the Tonic Regulation of the Pial Arteries, J. Neurol. & Psychiat. **1**:187, 1938.

16. Villaret, M., and Cachera, R.: L'embolie gazeuse; données expérimentales et pathogéniques, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:1093-1105, 1938.

17. Lewis, T.: Observations upon the Regulation of Blood Flow Through the Capillaries of the Human Skin, Heart **13**:1, 1926.

18. Krogh, A.: Handbuch der Gewebelehre des Menschen, Leipzig, Wilhelm Engelmann, 1930, p. 835.

reactions of vessels elsewhere than in the pia. Lewis,[17] in summing up these observations, concluded:

> The contraction of the minute vessels in response to tension after a short period of latency appears to be the direct result of stimulation of their walls. It is independent of nervous reflexes, central or local.

This statement seems true of the pial vessels, as noted by Fog.[14] Further support of this has been supplied by Forbes and associates,[11] who found the responses to a fall of systemic pressure preserved after local application of cocaine to the pia, whereas vasodilatation following stimulation of the geniculate ganglion was abolished.

In view of these observations it is interesting that vessel spasms dependent on a definite neurovascular mechanism are quite different in type (Ricker;[19] Chase[3b]). These authors have shown that an irritant, such as an air embolus, applied to a mesenteric vessel causes a local traumatic constriction which rapidly spreads peripherally to the terminal

Fig. 10.—Diagrams to explain the triangular shape of ischemic patches in the cortex on the basis of the anatomic distribution of the perforating arteries from the pia.

segments of the vessel, i. e., to the capillaries. Propagation of the constriction never occurs in such fashion in pial vessels, as already indicated.

It has been shown that areas of focal ischemia can be produced in the brain of cats by electrical or mechanical stimulation of the pial (and possibly the intracerebral) arterial vessels. This ischemia was brought about by vasoconstriction of these vessels and frequently occurred in the form of a triangular (or wedge-shaped) patch in the cortex (fig. 7). It is felt that the triangular shape of the ischemic patches is explained by the anatomic distribution of the perforating arterial vessels from the pia in each gyrus.

Diagrams *A* and *B* (fig. 10) illustrate this adequately. For instance, if the vessels over the surface of the central gyrus in diagram *A* are stimulated electrically they will be constricted and the greater part of the blood supply to the triangle shown in diagram *B* will be cut off. If only a few vessels are completely constricted on the surface of a gyrus the ischemia will be in the form of a smaller triangle, corresponding to

19. Ricker, G.: Relationspathologie, Berlin, Julius Springer, 1924.

the distribution of these vessels. At times, of course, the ischemia will be patchy, first, because the constrictions may be patchy and also because of the unevenness of the supply of collateral blood vessels. Patchy ischemia of this type would be expected to occur when stimulation was carried out so as to avoid applying the electrodes to the larger vessels. Even with this precaution, however, constrictions of the smaller vessels would, of course, result.

In the experiments described the observation was made that temporary focal cerebral ischemia from vascular spasm did not produce clinical evidence of epileptiform cortical discharges in cats recovered from ether anesthesia. This observation, however, does not prove that subclinical epileptiform discharges from cortical nerve cells were not taking place as a result of the ischemia. To test this possibility, recordings of the cortical potentials could be taken by means of the electroencephalograph during the period of cerebral ischemia. In this manner, the method reported in the present investigation might be used to test more fully the belief long held that temporary focal cerebral ischemia from vascular spasm may give rise to an epileptic seizure.

The clinical significance of the findings reported here must depend on whether the reactions of the cat's pial vessels are representative of what happens in the human brain. If they are one might have a partial explanation of the transitory paralysis that sometimes follows exposure and electrical stimulation of the human brain (at operation), the temporary paralyses following trauma and the mechanism concerned in electric shock. However, to apply observations made on the cat to the human subject is by no means wise, for it will be remembered that in this investigation it was noted that the dog's pial vessels are less sensitive to direct stimulation than the cat's and that the monkey's are even more refractory to this type of stimulation than the dog's. On the other hand, Riser [10] described the constriction of a single human pial vessel (to 20 per cent of its original diameter) on mechanical stimulation. That human vessels will contract vigorously is known also from the observations of Penfield,[20] for he has seen marked annular constrictions in human pial vessels following epileptic seizures.

A word of warning to physiologists appears justified in view of the observation that focal cerebral ischemia in the cat, and to a lesser degree in the dog and the monkey, can be produced with such ease by electrical stimulation of the pial vessels of the cortex. If this is not taken into consideration in experimental cortical stimulation, which it rarely seems to be, errors might be introduced in studying fatigue of nerve cells to electrical stimulation and in determining thresholds,

20. Penfield, W. G.: The Evidence for a Cerebral Vascular Mechanism in Epilepsy, Ann. Int. Med. **5**:303, 1933; The Circulation of the Epileptic Brain, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:605, 1938.

facilitation, extinction, blood flow and so on in the cortex. This fact might also be kept in mind during electrical stimulation of the human brain at operation.

SUMMARY AND CONCLUSIONS

The effects of mechanical and electrical stimulation on the pial vessels of 30 cats, 1 dog and 4 monkeys have been studied.

The pial vessels in cats contract vigorously on mechanical or electrical stimulation.

The dog's pial vessels are not as sensitive to this type of stimulation as the cat's; the monkey's are less so than the dog's.

Such evidence as there is suggests that these spasms are not dependent on a neurovascular mechanism. They resemble closely the local spasms in peripheral vessels described by Lewis and others as muscular, and not neuromuscular. They are localized to the site of stimulation and are not propagated, as are the neurovascular reactions described by Ricker and Chase in the mesenteric vessels of rabbits.

Mechanical stretch of the vessel wall appeared to be an adequate stimulus to produce vasoconstriction. This is direct evidence that the tone of a pial vessel, at least in the cat, may be partly maintained by a purely local mechanism, i. e., endovascular pressure (or stretch).

The effect of acetylcholine, amyl nitrate and carbon dioxide on constrictions in pial vessels (produced by local stimulation) was studied.

A method is described whereby temporary focal cerebral ischemia resulting from vasospasm may be produced in animals.

Diminished blood flow in the cortex, as a result of vasoconstriction of pial vessels, has been demonstrated by thermoelectric blood flow recording. Areas of focal cerebral ischemia, following constriction of pial vessels by electrical or mechanical stimulation, have been shown to be present by intravital staining. It has been demonstrated that these areas of focal ischemia are frequently wedge shaped and that this is due to the anatomic distribution of the cortical vessels.

No clinical evidence was found that temporary focal cerebral ischemia resulting from vasospasm in the temporal, parietal or occipital cortex of cats recovered from ether anesthesia gave rise to any epileptiform neuronal discharge. That subclinical neuronal discharges occurred as the result of ischemia could not be ruled out with the methods employed.

That electrical stimulation causes focal cerebral ischemia through spasm of vessels should be taken into consideration in certain physiologic problems in which the effect of electrical stimulation on cortical nerve cells is being studied.

A theoretic discussion of the findings with regard to their applicability to human vessels is presented, especially in relation to their possible significance in electrical stimulation of the brain at operation, in electric shock and in trauma to the head.

AVIAN THIAMINE DEFICIENCY

II. PATHOLOGIC CHANGES IN THE BRAIN AND CRANIAL NERVES (ESPECIALLY THE VESTIBULAR) AND THEIR RELATION TO THE CLINICAL BEHAVIOR

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In previous papers [1] the clinical and pathologic manifestations of a deficiency of thiamine in pigeons were described. Attention was directed chiefly to the peripheral nerves and the spinal cord, the brain and cranial nerves receiving relatively little consideration. For the sake of clarity and completeness this work will now be summarized. It will be unnecessary to survey the previous literature here, as that was done before.

The clinical manifestations in pigeons of a deficiency in thiamine were found to vary with the speed of onset of the deficiency. If birds were given a thiamine-free diet in amounts sufficient to prevent starvation, opisthotonos occurred. In these acutely deficient birds opisthotonos was usually attended by a few degenerating fibers in both the peripheral and the central nervous system, but in very acutely deficient pigeons degenerative changes were sometimes absent. On the other hand, if the ration was only partially deficient in thiamine (thiamine chloride was added to the diet), "locomotor ataxia," [2] and later leg weakness developed. These signs were accompanied by degeneration of the peripheral nerves, first of large proprioceptive nerve fibers and later of the medium-sized fibers, the small fibers usually remaining intact. Well defined and localized degeneration was present also in the brain and the spinal cord. When sufficient thiamine hydrochloride was added to the diet, regardless of the presence or absence of any other members of the B complex

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1. (*a*) Swank, R. L.: Avian Thiamin Deficiency: A Correlation of the Pathology and Clinical Behavior, J. Exper. Med. **71**:683, 1940. (*b*) Swank, R. L., and Bessey, O. A.: Avian Thiamine Deficiency: Characteristic Symptoms and Their Pathogenesis, J. Nutrition **22**:77, 1941.

2. A type of ataxia due to loss of postural sensibility. It is characterized by misplacing of the feet and buckling of the knees.

group of vitamins, the degenerating peripheral nerve fibers regenerated and, paralleling this, normal clinical behavior was restored.

The neuronal lesions attending "locomotor ataxia" and leg weakness involved first the axon at a point most distant from its cell body and progressed centralward. Degeneration of the myelin sheath followed. The largest fibers in the peripheral nerves were affected first, and degeneration of them frequently almost reached, but rarely entered, the dorsal ganglia. In no instance were degenerative lesions observed in or near the ventral roots of the spinal cord. The dorsal ganglion cells first shrank and later, when degeneration of their axons became severe, exhibited the axon reaction, which persisted after thiamine was given until the neurons regenerated and clinical rehabilitation was complete. A few neurons failed to recover and degenerated after four to seven weeks of restorative treatment. In Nissl preparations ganglion cells elsewhere in the central nervous system remained relatively unaffected by the deficiency. The central processes of the dorsal ganglion cells, which ascend the spinal cord in the dorsal funiculus, were thought to be unaffected, but in the present study, as will be shown later, many of their terminations in the nucleus cuneatus and nucleus gracilis did degenerate. Degeneration in these central terminations may have determined which dorsal ganglion cells did not recover.

Starvation control pigeons were also studied. In these "demyelination," accompanied by black staining of the myelin sheaths with the chlorate–osmic acid method, was noted. However, the axons remained intact, and no clinical symptoms developed. The mechanism by which starvation per se caused myelin sheaths to stain black with the Marchi method, and other factors, which have frequently led to misinterpretations, were discussed.

In the present study the brain and cranial nerves were studied in thiamine-deficient pigeons by methods which demonstrate the early changes in neurofibrils. The relation of these lesions to the clinical observations was considered.

DIETARY METHODS AND EXPERIMENTAL ANIMALS

The methods of caging and tube feeding the pigeons used in this study and the two thiamine-free diets (diets II and III) have been described.[1] Diet II contained 20 per cent casein (alcohol extracted), 65 per cent corn starch, 4 per cent cod liver oil, 6 per cent peanut oil, 4 per cent salt mixture and a vitamin K concentrate. As controls, about half of the total number of birds received diet III, which consisted of diet II plus 10 per cent autoclaved yeast. Each experimental bird was fed a daily maintenance ration of approximately 20 Gm. of one of the diets by tube, and thiamine hydrochloride (Merck) was omitted from or

added to the ration in small amounts in order to produce acute or chronic thiamine deficiency as desired. As the results obtained with the two diets were the same, the two groups of animals will be presented and discussed together.

In accordance with the general dietary methods outlined before,[1a] the experiments have been grouped as follows, depending on whether the birds were (1) very acutely deficient in thiamine, (2) moderately acutely deficient in thiamine, (3) chronically deficient in thiamine or (4) restored: 1. The very acutely deficient group corresponded to the acutely deficient birds in the former study.[1a] They were fed 15 to 20 Gm. of diet III plus 25 micrograms of thiamine hydrochloride daily for three weeks. The thiamine hydrochloride was then discontinued and diet II substituted for diet III in order to make the diet as free of thiamine as possible. In seven to nine days opisthotonos appeared suddenly. 2. The group of pigeons with moderately acute deficiency received the same dietary treatment prior to withdrawal of thiamine hydrochloride. Thiamine was then discontinued, and the diet (diet III) was reduced to 10 to 15 Gm. daily so that the deficiency would develop somewhat less rapidly. These birds showed opisthotonos in nine to twelve days. The preliminary dietary management in the acute experiments appeared to make the pathologic changes very uniform, so that only early changes were present in pigeons with very acute deficiency and easily evaluated later changes were seen in pigeons with moderately acute deficiency. The pigeons with chronic deficiency received daily 20 Gm. of diet plus 15 to 20 micrograms of thiamine hydrochloride. Most of these manifested "locomotor ataxia," cerebellar ataxia [3] and (or) cardiac failure, and a few had terminal opisthotonos. All pigeons were restored by giving them 100 micrograms of thiamine hydrochloride every other day plus diet II or III or normal grain. Starvation controls were not studied, for, as shown before,[1a] starvation affects only the myelin sheaths and in this study we are primarily interested in changes in the axons and the cell bodies.

HISTOLOGIC TECHNIC

The experimental observations included in this paper were made on a total of approximately 90 thiamine-deficient pigeons, 70 of which were studied histologically. Normal control pigeons were studied by the same methods. The brains of 35 of the pigeons were fixed in 50 per cent alcohol and 10 to 20 per cent chloral hydrate for twenty-four hours. The petrous bones (which contain the peripheral nerve endings of the vestibular and cochlear nerves) from these birds and, in addition, the intact brains and skulls from 15 other pigeons were fixed in the same solutions to which 2 or 3 per cent nitric acid had been added (de Castro

3. This is distinct from "locomotor ataxia" and is characterized by staggering.

technic). This method of simultaneously decalcifying and fixing the intact specimen in twenty-four to forty-eight hours proved superior to all other methods of fixation tried on our material. All specimens were then cut into suitable blocks, washed a few hours in water and placed for twenty-four hours in 96 per cent alcohol containing 4 drops of ammonium hydroxide per hundred cubic centimeters. After drying with filter paper they were transferred to a 2 per cent aqueous solution of silver nitrate for six to seven days (or until the desired brown color was present in the tissues). This solution was changed frequently and was kept in an incubator at a temperature of 37 C. The tissues were then washed a few minutes and reduced in a 2 per cent solution of hydroquinone plus an 8 per cent concentration of solution of formaldehyde U. S. P. for thirty-six hours at room temperature. They were next washed in water, embedded in paraffin (using the dioxane method), sectioned serially and mounted without gold toning. Pieces of cerebellum were sectioned both transversely and longitudinally.

The cerebellums of 20 other pigeons that had acute or chronic deficiency or that had been deficient and then partially or completely restored to normal by administration of thiamine were fixed in solution of formaldehyde. They [4] were longitudinally sectioned while frozen and impregnated according to the well known method of Ramón y Cajal for frozen sections and the double impregnation method of del Río Hortega for nerve fibers. Cajal's method was utilized as follows: Sections 20 microns thick were washed in water and placed for four hours in a solution consisting of 10 cc. of 2 per cent silver nitrate, 7 to 8 drops of pyridine and 6 cc. of 96 per cent alcohol. Each section was then washed for two seconds in 96 per cent alcohol and reduced for two to three minutes in 0.3 Gm. of hydroquinone, 70 cc. of distilled water, 20 cc. of solution of formaldehyde and 15 cc. of acetone. They were carefully washed three times in water, toned in gold and fixed as usual and mounted in xylene balsam. The double impregnation method (slightly modified) was used as follows: Sections which had remained in the aforementioned Cajal solution of silver nitrate for four to twenty-four hours were rapidly washed in water and placed in a 5 per cent solution of silver carbonate at a temperature of 60 C. until the sections became dark brown. They were then washed in water and reduced in dilute solution of formaldehyde U. S. P. (1:10), gold toned and fixed as usual and mounted as already described.

In addition to the pathologic studies, which were concerned primarily with alterations in the neurofibrils of nerve cells and their processes,

4. These were cerebellums from a few of the pigeons studied previously.[1a] Dr. Wolbach allowed these tissues to be used in this study.

the behavior of both acute and chronically deficient pigeons was closely observed. These clinical observations will be presented first and will be followed by descriptions of the changes which appeared in acutely and chronically thiamine-deficient pigeons and in others restored to normal from these degrees of the deficiency. Finally, small hemorrhagic lesions observed in a few pigeons will be mentioned.

RESULTS

BEHAVIOR OF THIAMINE-DEFICIENT PIGEONS

It was pointed out in the introduction [1] that chronically deficient pigeons acquire "locomotor ataxia" [2] and weakness of the legs as a result of degeneration of peripheral nerve fibers. When mild, pigeons with this type of ataxia were sometimes restored to normal in two to three days by the administration of thiamine hydrochloride, but when the ataxia was more severe restoration required one to three weeks. When marked muscular weakness was also present, so that the animals were unable to support their own weight, restoration to normal was frequently delayed for seven to nine weeks.

Staggering was also noted in thiamine-deficient pigeons; it was usually associated with "locomotor ataxia" and was not explained pathologically in the previous study. Frequently it appears hours or days before opisthotonos or precedes the onset of "locomotor ataxia" in the more chronic experiments. It rarely exists alone for more than a few days, and pigeons without are usually restored to normal in several to twenty-four hours by adequate injections of thiamine hydrochloride. Because of the lesions associated with the staggering, it will be referred to as cerebellar ataxia.[3]

In acute experiments opisthotonos may develop rather abruptly or be preceded by a characteristic series of movements, now to be described. These are usually initiated by periodic, rhythmic lateral rotation of the head to one side or alternately from one side to the other. Soon this becomes accompanied, and later replaced, by extensor thrusts of the neck. At first the head is flexed but later extends synchronously with the movements of the neck. Extension of the head and neck soon becomes more marked, eventually loses its rhythmic nature, and tonic opisthotonos results. Backward rolling of the animal accompanied by vigorous flapping of the wings may occur, but usually the position of opisthotonos, without rolling, predominates. When opisthotonos becomes fully developed the legs may be flaccid and held rigidly in a flexor position or in an extended position with the claws spread apart, as they are when the animal stands. Periodic transient relaxation of the opisthotonos may occur. It should be remembered that the movements

preceding tonic opisthotonos are in a constant state of flux. The development of opisthotonos may be interrupted spontaneously at any time and normal behavior established, especially when concomitant starvation exists. This is usually followed, after a variable interval, by vigorous opisthotonos.

If at any time during the sequence of changes leading to opisthotonos the pigeon is rotated rapidly through space for a few seconds, the rhythmic head movements may be exaggerated, much as lateral gaze or rotation in human subjects brings out nystagmus. This increased activity lasts but a few seconds. Normal or deficient pigeons without rhythmic forced movements of the head are unaffected by this procedure. The similarity of the rhythmic head movements in thiamine-deficient pigeons to those observed after destruction of one labyrinth in normal birds will be discussed later.

Another symptom, so-called enopisthotonos,[5] is occasionally observed in acutely thiamine-depleted pigeons but is seen more frequently in chronically deficient birds after the thiamine intake has been suddenly discontinued. Many of these have cardiac failure.[1a] Lateral rotation and extensor movements of the head, indistinguishable from the movements preceding opisthotonos, frequently antedate the onset of enopisthotonos. Soon the extensor movements become weaker and disappear, and the head and neck droop forward in the position of enopisthotonos. A bird then seems unable to elevate its head above a horizontal plane, although lateral rotation does occur and extension of the neck may be attempted. This symptom may also be a sequel to opisthotonos. A pigeon with enopisthotonos is usually quite unresponsive to visual or auditory stimulation but responds weakly to touch, and it frequently survives but a short time even when treated. When an injection of thiamine is given, opisthotonos may develop in thirty to sixty minutes and the bird then recover.

ANATOMIC CONSIDERATION

The present study deals with the changes which occur in the brain and cranial nerves of thiamine-deficient pigeons, the most important of which were found in the vestibulocerebellar system. As the anatomy and physiology of this system in birds are unsettled, we propose now to summarize the more important information, in order to facilitate later descriptions and obviate misunderstanding. Our conception of this material, based on an analysis of the literature and our own observations, is presented diagrammatically in figure 1, *A* and *B*.

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5. This symptom was observed infrequently in the present series of experiments, so that satisfactory material for histologic study was not available. Most of its clinical characteristics were determined during previous studies.[1]

The central portion of the cochlear division of the eighth nerve [6] pierces the dorsolateral aspect of the medulla and ends in the nucleus angularis and the nucleus magnocellularis, entering the latter nucleus on its dorsolateral surface. Many fibers arising from the nucleus magnocellularis then cross the midline in the dorsal decussation and terminate in the contralateral nucleus magnocellularis and nucleus laminaris, and others go to the homolateral nucleus laminaris. The peripheral processes of bipolar cells of the spiral ganglion [7] terminate as pericellular baskets or intracellular plexuses in the sensorial epithelium of the cochlea. The cochlear nerve cells, their central and peripheral processes and the nerve endings in the cochlea are of medium size with respect to the corresponding parts of the large vestibular nerve fibers.

From Scarpa's ganglion the central processes of the vestibular nerve enter the medulla just ventral and cephalad to the cochlear nerve. The vestibular nerve is large and composed of two types of fibers, large and small, the large fibers being very thick and the more important in this study. According to Cajal,[9] who studied bird embryos and very young birds, the more important collaterals and terminations of the large fibers are as follows (solid lines in figure 1): (1) collaterals to a group of ganglion cells just inside the medulla, referred to as the tangential nucleus; (2) descending fibers to the nuclei of the sixth and twelfth cranial nerves; (3) the homolateral and contralateral medial longitudinal bundles; in which many fibers descend into the cervical portion of the spinal cord to terminate in the ventral gray columns and a few ascend to the nucleus of the fourth cranial nerve (according to Winkler,[10] others continue to the nuclei of the third cranial nerve); (4) the region occupied by the large nerve cells in the homolateral and contralateral reticular formations; (5) homolateral and contralateral fibers to Deiters' nuclei; (6) the cerebellar cortex, and (7) collaterals from fibers going to Deiters' nuclei to the vestibulocerebellar and cerebellar nuclei (bigeminal nuclei).

Winkler, using the Marchi method after the cochlea had been destroyed or the vestibular nerve cut central to Scarpa's ganglion, was able to trace both direct and crossed fibers into each nucleus magno-

6. Wallenberg, A.: Ueber zentral Endställen des Nervus octavus der Tauben, Anat. Anz. **17**:102, 1900. Turner, C. H.: Morphology of the Avian Brain, J. Comp. Neurol. **1**:39, 1891; cited by Ramón y Cajal.[9]

7. Ramón y Cajal, S.: Terminación periférica del nervio acústico de las aves, Trab. d. Lab. de invest. biol. de la Univ. de Madrid **6**:161, 1908.

8. Footnote deleted.

9. Ramón y Cajal, S.: Les ganglions terminaux du nerf acoustique des oiseaux, Trab. d. Lab. de invest. biol. de la Univ. de Madrid **6**:195, 1908.

10. Winkler, C.: The Central Course of the Nervus Octavus and Its Influence on Motility, Verhandl. d. k. Akad. v. Wetensch. **14**:1, 1907.

cellularis. The direct fibers entered the ventral surface of the nucleus from the ventrolateral direction, and the crossing fibers helped to form a well developed bundle in the midline (the dorsal crossed bundle) and then entered the ventral surface of the nucleus magnocellularis from a ventromedial direction. Our observations support the conclusions of Winkler (the connections are indicated by broken lines in figure 1 *B*). Thus the nucleus magnocellularis seems to receive two types of fibers—

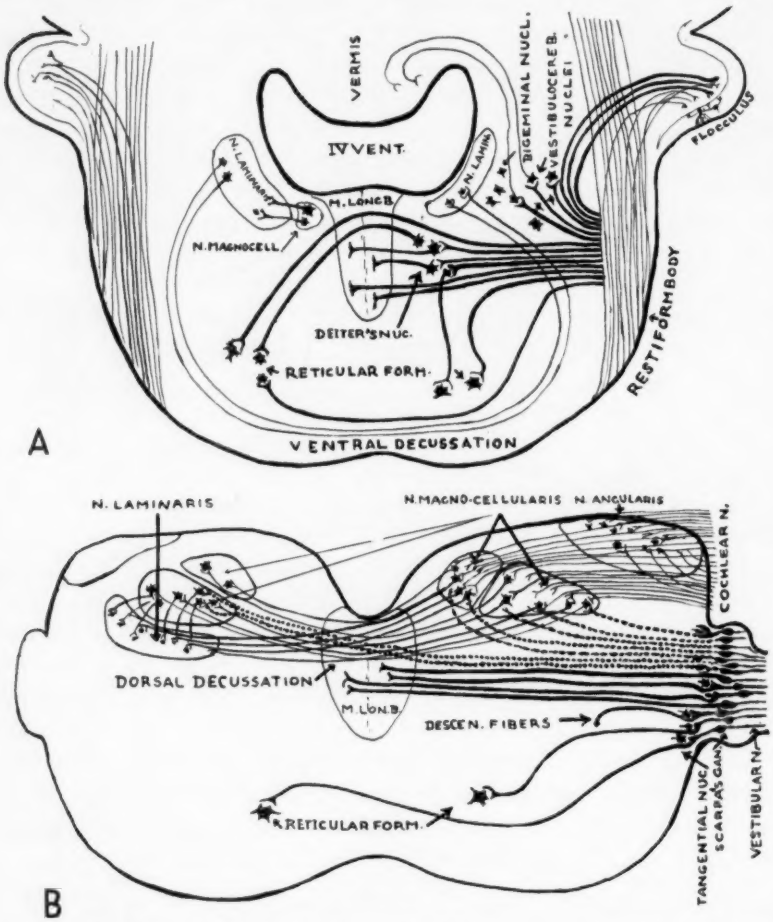

Fig. 1.—Schematic illustration of the central terminations of the eighth nerve and several of its more important secondary connections. This is based on an analysis of the literature and our own observations. Section *A* is above Scarpa's ganglion at the level of the cerebellar flocculus and the nucleus laminaris. Section *B* is at the level of Scarpa's ganglion and the nucleus magnocellularis. The fine lines indicate cochlear nerve connections and the heavy lines vestibular nerve connections. The heavy broken lines represent the connections described by Winkler and the heavy lines the connections described by Cajal.

the medium-sized cochlear fibers by its dorsal and dorsolateral surfaces and the large vestibular fibers by its ventral surface. In slightly oblique sections through the medulla the nucleus magnocellularis appears to be clearly divided into a medial and a lateral portion. Another dissociated group of similar cells surrounded by cochlear fibers is located still further lateralward. In addition to sending many fibers to the nucleus laminaris on both sides, the nuclei magnocellulares exchange many fibers which help to form the dorsal crossed bundle (dorsal cochlear decussation).

Cajal denies that the nucleus magnocellularis receives vestibular fibers, claiming that the degeneration traced into one nucleus magnocellularis was due to trauma inflicted on the opposite nucleus magnocellularis or to other nuclear masses. This does not appear to explain the origin of the degenerating fibers which entered the homolateral nucleus magnocellularis by its ventral surface. Furthermore, these

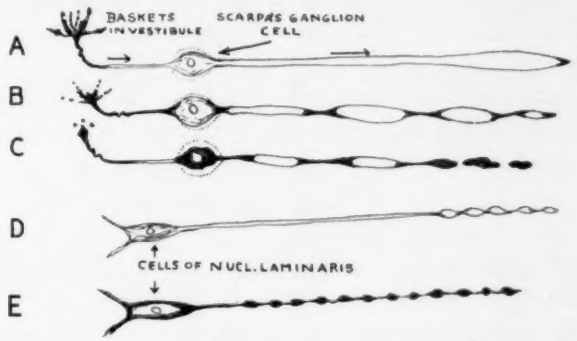

Fig. 2.—Schematic representation of the progression of degeneration in large (*A*, *B* and *C*) and medium-sized (*D* and *E*) neurons in pigeons with moderately acute thiamine deficiency.

nerves are of large size, more in keeping with the caliber of vestibular fibers.

Recent investigations by Larsell, Dow [11] and others have shown that vestibular fibers proceed directly to the flocculonodular lobe of the cerebellum. This part of the cerebellum also receives many secondary connections of the vestibular system. In our preparations direct fibers could be followed to the flocculus in large numbers. The nodulus appeared, however, to receive mostly secondary vestibular fibers from the vestibulocerebellar nuclei of Cajal.

The peripheral processes of the vestibular nerve [9] pierce the bony labyrinth at the cristae, which are arranged as in other species, and

11. Larsell, O.: The Cerebellum: A Review and Interpretation, Arch. Neurol. & Psychiat. **38**:580 (Sept.) 1937. Larsell, O., and Dow, R. S.: The Development of the Cerebellum in the Bat and Certain Other Mammals, J. Comp. Neurol. **62**:443, 1935.

supply the overlying sensorial epitheliums, and as well the utricle and saccule, with two types of nerve terminations. The first are pericellular baskets formed on the crown of the crista by very large fibers and on the sides of the crista by slightly smaller fibers. The second are intraepithelial plexuses formed by small fibers. The anterior and posterior cristae were easily identified in our preparations and, with the urticles, appeared to be of major importance in this study. Also of considerable interest in the present study was the fact that the peripheral vestibular nerve to the posterior crista was about 80 per cent longer than the nerve to the anterior crista; the former measured approximately 1.8 mm. and the latter 1 mm. (an average of crude measurements with a micrometer mechanical stage on 4 different specimens).

One secondary vestibulocochlear center,[12] the nucleus laminaris, is worthy of mention. It is situated mainly rostral to the nucleus magnocellularis, from which it receives many homolateral and contralateral fibers. Each nucleus laminaris sends fibers streaming ventrally to help form the ventral decussation (trapezoid body of Cajal[9]).

The arrangement of nerve cells and fibers in the cerebellar cortex and the source of incoming cerebellar nerve fibers, i. e., the spinocerebellar tract, need no especial attention.

PATHOLOGIC OBSERVATIONS

The character of the axonal changes and their distribution in the brain and the cranial nerves will now be described.

A. Lesions Produced by Thiamine Deficiency in Axons and Their Trophic Cell Bodies.—These lesions are of the same general type wherever observed. They are modified, but not fundamentally changed, by the conditions of the experiment or their anatomic location. In pigeons with moderately acute deficiency the following changes, characteristic for large fibers, were consistently noted in the cell bodies of Scarpa's ganglion and in their central and peripheral terminations. Generalized swelling and thickening of the neurofibrils of the terminal portion of these axons (figs. 2 *A*, 3 *B* and *C*) constituted the first dependable histologic change. Simultaneously their trophic cell bodies appeared normal or were slightly shrunken, and the staining of the entire neuron by the Cajal method had a tendency to be pale. More intensely stained constrictions soon appeared in the swollen parts of the axons, with the production of many varicosities (figs. 2 *B*; 3 *A*, *B* and *C*; 4 *C*, and 5 *C*). Next their distal portions became irregular, more intensely stained and

12. Because our studies indicated that the auditory and the vestibular nuclei cannot be clearly separated anatomically, we have preferred to designate these secondary centers by the mixed term vestibulocochlear nuclei.

finally fragmented (figs. 2 *C*; 3 *E*; 5 *A*, *B* and *E*). While these changes were taking place distally, less marked but similar alterations occurred in the axon nearer the trophic cell body: The cell bodies continued to shrink, and many came to stain intensely, exhibiting the changes referred to as sclerosis (figs. 2 *C*; 3 *A* and 4 *D*). The axon reaction was observed infrequently in Scarpa's ganglion or elsewhere.

Medium-sized fibers, such as those forming the trapezoid body, were affected later than the large ones. They had a tendency to form many marked constrictions or varicosities, which gave their axons the appearance of a string of oval beads (fig. 3 *D*). Although medium-sized axons were altered in their distal parts first (fig. 2 *D*), they frequently came to appear uniformly changed throughout their length (fig. 2 *E*), and few of them fragmented. Their trophic cell bodies exhibited no, or but slight, changes. Thus the large fibers have a tendency to fragment early and form few varicosities and the medium-sized fibers to fragment late and to form many varicosities.

The character of the axonal changes was altered somewhat by the speed of onset of a thiamine deficiency. If the depletion developed slowly (chronic deficiency) the axonal swelling was marked and varicosities were numerous even in the large fibers. Strangely enough, in such chronic preparations marked changes throughout the entire length of the axon usually developed without great change appearing in the trophic cell body (fig. 4 *B*, *C* and *D*). Conversely, in the cases of more acute deficiency fewer varicosities developed, and initial slight swelling was followed soon by fragmentation of the distal part of the axon and by definite changes in the cell body. In a few instances in which the onset of the deficiency was very acute, necrosis of the cell body and of its axon appeared to occur simultaneously (fig. 7 [1a]). This type of change was seen infrequently in pigeons but was observed in the cerebral cortex of 4 kittens with very acute thiamine deficiency.

B. Intensity and Distribution of Degenerative Changes in Very Acutely Deficient Pigeons with Opisthotonos.—The character of the lesions in 4 of the birds (pigeons 40, 41, 39 and 37) in this group is represented in the table. The lesions consisted chiefly of swelling, formation of varicosities and thickening of neurofibrils (indicated by + in the table) and were confined to the terminations of the axons (fig. 2 *A*). These changes were observed in the central vestibular terminations, chiefly in the nucleus magnocellularis and the flocculus of the cerebellum, and less frequently in the terminations in the reticular formation and the vestibulocerebellar and related nuclei. Slight changes might have been present in the medial longitudinal bundle or in the descending fibers to the nuclei of the sixth and twelfth cranial nerves and have failed detection, as degenerating fibers were seen with difficulty in cross sec-

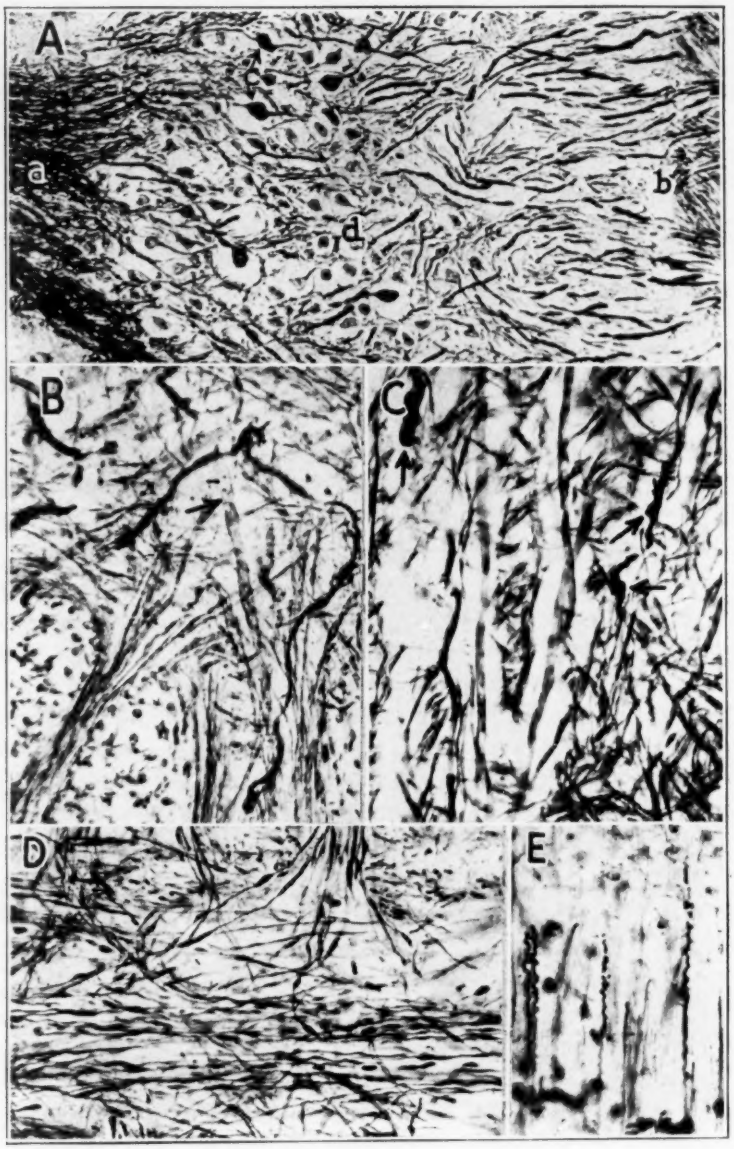

Figure 3

(See legend on opposite page)

tion (only from chronic preparations were longitudinal sections made). Cellular changes were limited to slight shrinkage (+) of a few cells in Scarpa's ganglion. Inconsistent early changes were observed in the basket terminations and moss fibers of the cerebellum, and in 1 instance (pigeon 39) many basket axons and terminations were fragmented. Unfortunately, the peripheral endings of the vestibular nerve fibers in the sensorial epitheliums of the labyrinths failed to stain satisfactorily in any of this group of pigeons.

The optic system, except in 1 instance (pigeon 39, in which the cellular changes were graded +), was free of change, as were the secondary vestibulocochlear centers. In several very acutely deficient pigeons no significant changes were observed.

C. Severity and Distribution of Degeneration in Pigeons Showing Moderately Acute Deficiency with Opisthotonos.—The character of the lesions in this group (pigeons 59, 57, 54, 29, 18, 32 and 48) is also represented in the table. Advanced and widespread changes (+ + +) were present in the peripheral terminations of the vestibular nerve to the labyrinth, in the central terminations of this nerve to the nucleus magnocellularis and in the basket fibers of the cerebellum. Elsewhere (table) the axonal changes were early (+) and much less conspicuous. Many cells in Scarpa's ganglion (fig. 3*A*) and in the lateral portion of the nucleus magnocellularis (fig. 4*A*) were slightly shrunken (+) to sclerotic (+ +), and mild cellular changes, similar to those shown

EXPLANATION OF FIGURE 3

A, Scarpa's ganglion from a pigeon with moderately acute thiamine deficiency (Cajal block stain; × 200). At *a* the peripheral vestibular nerve enters the petrous process of the temporal bone, and at *b* the central processes enter the medulla. Note sclerosed ganglion cells at *c*, relatively normal cells (perhaps slightly shrunken) at *d* and varicosed axons.

B, dorsal part of the median raphe (dorsal vestibular decussation) in a pigeon with moderately acute thiamine deficiency, showing various degenerative changes in large axons (Cajal block stain; × 320). Note swollen and pale-stained axon (arrow) and dark-stained and varicosed axons.

C, region of Deiters' nucleus in a pigeon with moderately acute thiamine deficiency (Cajal block stain; × 320). Here the changes are similar to those shown in *B*. Note darkly stained, varicosed axons and others beginning to fragment (arrows).

D, ventral part of the median raphe, showing many decussating medium-sized fibers from the trapezoid body in a pigeon with moderately acute thiamine deficiency (Cajal block stain; × 375). Note darkly stained fibers with abnormal varicosities.

E, optic lobe from a pigeon with moderately acute thiamine deficiency (Cajal block stain; × 320). Note the very tortuous and fragmented axons.

*Relative Intensity and Distribution of Degenerative Lesions in the Peripheral and Central Terminations and Cell Bodies of the Vestibular Nerve, in Certain Secondary Centers of the Eighth Cranial Nerve, in the Cerebellar Basket Fibers and Spinocerebellar Fibers and the Optic Nerve System in Pigeons with Very Acute, Moderately Acute and Chronic Thiamine Deficiency**

		Cerebellum							Secondary Centers of viii Nerve			Vestibular Nerve												
		Optic Lobe		Basket Cells		Spinocerebellar Fasciculus						Central Terminations										Peripheral Portion		
Type of Deficiency	Pigeon	Subtectum	Tectum	Axons	Basket Terminations	Climbing Fibers	Moss Fibers	Restiform Body	Trapezoid Body	Nucleus Parvocellularis	Nucleus Magnocellularis	Vestibular Cerebellar and Bigeminal Nuclei	Cerebellar (Flocculus Lobe)	Deiters' Nucleus	Reticular Formation	Descending Fibers to VI and XII Cranial Nerves	Medial Longitudinal Bundle, Ascending	Medial Longitudinal Bundle, Descending	Nucleus Magnocellularis, Medial Portion	Nucleus Magnocellularis, Lateral Portion	Tangential Nucleus	Scarpa's Ganglion Cells	Distal Axon	Vestibule
Very acute	40	0	0	0	+	0	+	0	0	0	0	0	+	0	0		0	0	0	+|	0	0	0	
	41	0	0	0	0		0	0	0	0	0	+	+	0			0	0	+	+	0	+	0	
	39	+	0	+	++	+	+	0	0	0	0	+	+	+	+		0	0	+	+	0	+	0	
	37	0	0	0	0			0	0	0	0	0	+	0	0		0	0	+	+	0	+	0	
Moderately acute	59	+	+				++	0	+	0	0	+	++	+	+	+	+	+	+	++	0	++	++	++
	57	0	0					0	+	0	0	+	+	+	++	+		+	+	+++	0	+	0	++
	54	++	0	++	++		+	0	+	0	0	+	+	++	+				+	+++	0	+	+	+++
	29	++	++	++	+++	|+	+	0	+	0	+			+	+	+			+	++	0	++	0	
	18	+	|+				0	0	+	0	+	+	+	+	+		0	0	+	++	0	+	+	++
	32			++	+++		++																	
	48			++	+++		++																	
Chronic	15	+	+	+	+		+		+		|+		+	+	++	+		++	+	+	+	+	0	+
	8	+	+				+++	++	++	+	+	++	++	+++	++		++	+++	++	+++	++	+	+	++
	9			++	++++		+++	+++									++	+++						+
	20			+	+++			0		0	|+	+	+	+		++	+	++	++	++++		+		+++
	179				++																			

* The horizontal columns labeled Scarpa's ganglion, nucleus magnocellularis and nucleus parvocellularis refer to the ganglion cells in these regions. With reference to these cells, + indicates slight shrinkage and ++ indicates marked shrinkage with thick and darkly stained neurofibrils (sclerosis). The remaining columns refer to axons and their terminations. The one labeled "Vestibule" refers to the basket terminations in the vestibules, and the column just below "Distal Axon" to the vestibular nerve proximal to this. The tectum includes the superficial layers of the optic lobes, and the subtectum refers to deeper structures, as indicated in the text. The climbing and the moss fibers have been grouped together under the spinocerebellar fasciculus, although, as indicated in the text, we feel that the moss fibers are the main, if not the only, terminations of the spinocerebellar fibers. All other notations in the table need no further comment. With reference to cell processes, + indicates thickened neurofibrils and generalized swelling of nerve fibers, with beginning formation of varicosities; ++ indicates that a few fibers have fragmented, +++ that many fibers have fragmented and ++++ that few nonfragmented fibers remained, 0 indicates no degenerative change, and a blank space indicates that for technical reasons no evaluation could be made.

in figure 4 *B*, were seen in the reticular formation. Interestingly enough, reticular cells in the upper portion of the brain stem suffered less than those at the level of entrance of the vestibular nerves.

The peripheral terminations of the vestibular nerve in the cristae suffered changes similar to those observed elsewhere, namely, swelling and fragmentation. The swelling was slight in these acutely deficient birds, and fragmentation occurred early, so that many endings disappeared. The lesions were most marked at the tops of the cristae (fig. 7 *A* and *B*), where all endings had disappeared in a few instances, and were least marked on the sides of the cristae near the base. In 6 birds degeneration was more marked in the posterior crista (fig. 7 *A*) than elsewhere in the labyrinth (see anterior crista for comparison, fig. 7 *B*). One posterior or anterior crista might be affected more than the corresponding contralateral crista, and slight, variable changes were present in the other sensorial epitheliums of the labyrinths. As the vestibular nerve fibers entered the bony cristae they were slightly swollen and tortuous and their neurofibrils thickened, but proximal to this point they were essentially normal (pigeons 54 and 18 were exceptions).

Many fragmented axons (+ + +) entered the ventral surface of the lateral portion of the nucleus magnocellularis from both a medial and a ventrolateral direction (figs. 4 *A* and 5 *A*). The medial portion of this nucleus received many axons with less advanced changes. In its lateral portion were many (shrunken and sclerotic) ganglion cells (fig. 4 *A*), and from these, and other cells in the medial portion of the nucleus, which appeared normal, axons with early changes similar to those in figure 4 *C* could be traced ventromedially into the dorsal crossed bundle. According to Cajal and others, many of these axons terminate in the opposite nucleus magnocellularis and in the homolateral and the contralateral nucleus laminaris.

Earlier (+) and less extensive changes were observed in the remaining central terminations of the vestibular nerve (table) and in the medium-sized fibers which arise from normal-appearing cells in the nucleus laminaris. Many of the latter fibers helped to form the trapezoid body (ventral vestibulocochlear decussation), and others entered into the formation of the ventral part of the median raphe (fig. 3 *D*).

The cerebellar changes were marked in these birds. Many basket fibers were swollen and their terminations as baskets around the Purkinje cells fragmented (+ + +; figs. 6 *E, F, H, I* and *J*). This was very marked at the tops of the cerebellar convolutions and minimal at the bases of the convolutions, deep in the fissures. The Purkinje cells and axons, however, were normal. Early (+) and moderately advanced (+ +) degenerative changes were also seen in the moss fibers (fig. 6 *C*), these being most evident at the tops of convolutions just below the Purkinje layer of cells (for topography see fig. 6 *D*).

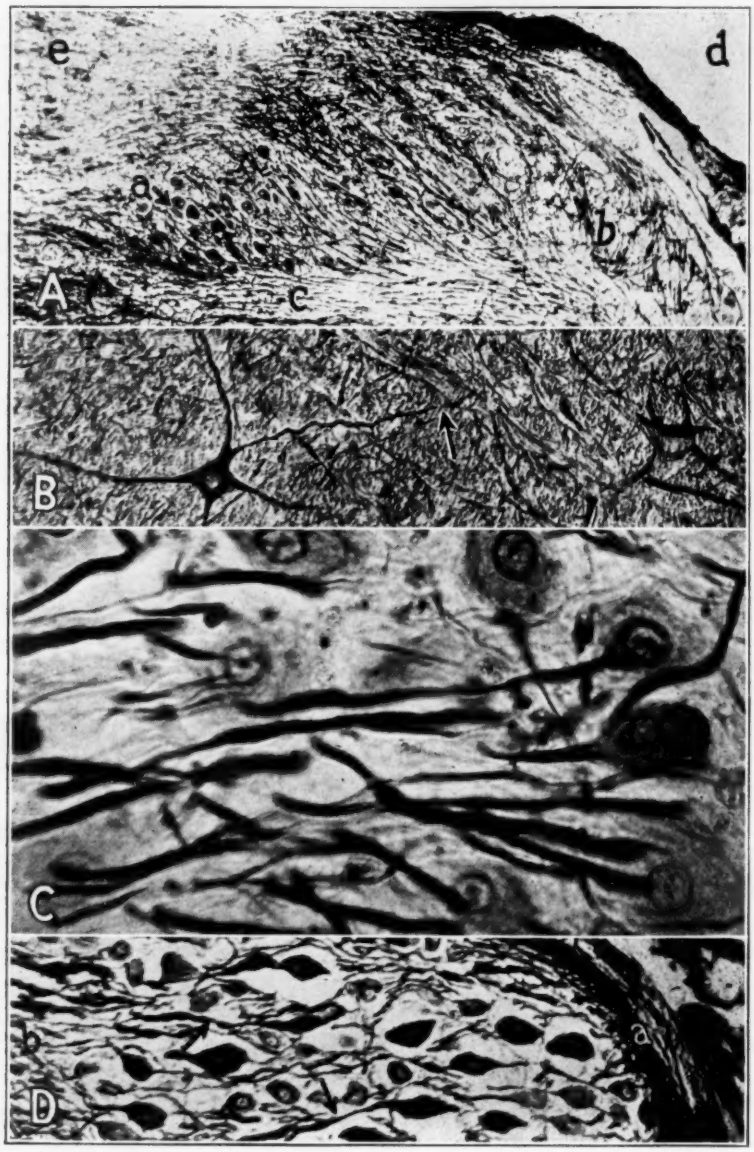

Figure 4

(See legend on opposite page)

The lesions in the vestibulocerebellar system just described were present in all pigeons with moderately acute deficiency. Less constant changes were observed in the optic system, in the superficial layers of the tectum (fig. 3 *E*), in subtectal regions (isthmus nucleus and tectospinal tract), in the pretectal regions near the formation of the posterior commissure (fig. 7 *C*), in the nucleus rotundus of the thalamus, in the decussation of the superior colliculi (see Papez [13] for terminology) and occasionally elsewhere.

D. Intensity and Distribution of Degenerative Changes in Chronically Deficient Pigeons.—The nature of such lesions is represented by pigeons 15, 8, 9, 20 and 179, as indicated in the table. In contrast to the unequal distribution of degeneration in the acutely deficient pigeons, the most notable pathologic feature in the chronically deficient pigeons without opisthotonos, but with ataxia and other chronic symptoms (pigeons 15, 8, 9 and 179), was a tendency for all the central and the peripheral terminations of the vestibular nerve to exhibit changes of nearly equal severity (fig. 5 *B, C* and *E*). Also, many axons had degenerated to a point much nearer their trophic cell bodies. This is illustrated by degeneration in the collaterals to the tangential nucleus (fig. 5 *B*). A similar tendency in other large nerve fibers is shown by degeneration of the spinocerebellar fibers in the restiform body (fig. 5 *D*).

There were fewer degenerating fibers in the labyrinth and in the nucleus magnocellularis in the chronically deficient animals without opisthotonos than in the acutely deficient pigeons. Many peripheral terminations

13. Papez, J. W.: Comparative Neurology, New York, Thomas Y. Crowell Company, 1929.

EXPLANATION OF FIGURE 4

A, nucleus magnocellularis in a pigeon with moderately acute thiamine deficiency (Cajal block stain; × 98). Note the darkly stained, sclerosed ganglion cells in the lateral part of the nucleus, at *a;* the normal, lightly stained cells in the medial part of the nucleus, at *b*, and the fragmented axons entering the lateral part of the nucleus, at *c*. At *d* is the fourth ventricle and at *e* the cochlear nerve.

B, reticular formation in a pigeon with chronic thiamine deficiency (Cajal block stain; × 172). Note two large neurons exhibiting thickened and heavily stained neurofibrils. The axon of one cell is fragmented (arrow).

C, nucleus magnocellularis in a pigeon with chronic thiamine deficiency (Cajal block stain; × 500). Note the relatively normal-appearing cells from which arise processes exhibiting early degenerative changes.

D, Scarpa's ganglion from a pigeon with chronic thiamine deficiency (Cajal block stain; × 200). Note the marked axonal changes (arrows) and shrunken and sclerosed ganglion cells. No cells exhibit the axon reaction. The petrous bone is shown at *a*, and central processes of ganglion cells enter the medulla at *b*.

Figure 5

(See legend on opposite page)

of the vestibular nerve in the labyrinth became markedly swollen (fig. 7 *D*) without fragmenting, and many fragmented nerve endings regenerated, while others in the same microscopic field appeared to be degenerating (fig. 7 *E*). In 2 chronically deficient pigeons, one with frequent periodic opisthotonos (pigeon 20) and the other with opisthotonos (not included in the table) for five days despite administration of many large doses (200 micrograms) of thiamine hydrochloride, the changes in the vestibule and in the axons entering the ventral surface of the nucleus magnocellularis were extreme (+ + + +). This, again, points to the close anatomic and physiologic relation of these two regions in the pigeon and their importance in the production of opisthotonos.

There was an increased number of fragmented moss fibers in the cerebellum and degenerating axons in the restiform body (fig. 5 *D*). The number of degenerating basket fibers was not significantly increased, but many had now disappeared (fig. 6 *D* and *G*). In a few cases (of acute as well as of chronic deficiency) in which marked degeneration was present in the basket terminations early changes were observed in the parallel fibers arising from the granule cells. There was definite swelling of the axons arising from normal-appearing Purkinje cells (fig. 6 *D*) in the more chronically deficient pigeons. These changes were more noticeable near the apexes of the convolutions.

Less constant axonal lesions were observed in other regions of the brain in chronically deficient birds. Because of their connections with the vestibular system, changes in the oculomotor and trochlear nerves and their nuclei are of most interest. These consisted mainly of early, and occasionally of late, changes in the axons and sclerosis of the ganglion cells. The optic system exhibited slightly more advanced lesions

EXPLANATION OF FIGURE 5

A, region of the nucleus magnocellularis in a pigeon with moderately acute thiamine deficiency (Cajal block stain; × 490). Note the large number of fragmented axons at *a* which enter the nucleus magnocellularis (*b*).

B, tangential nucleus in a pigeon with chronic thiamine deficiency (Cajal block stain; × 675). Note the degenerating vestibular nerve collateral (arrow) in contact with a ganglion cell and another degenerating collateral in the lower part of the photograph (arrow).

C, flocculus of cerebellum in a pigeon with chronic thiamine deficiency (Cajal block stain; × 325). Note degenerating vestibular nerve fibers (arrows).

D, restiform body in a pigeon with chronic thiamine deficiency (Cajal block stain; × 325). Note the large number of fragmented spinocerebellar fibers.

E, median longitudinal bundle below Scarpa's ganglion in a pigeon with chronic thiamine deficiency (Cajal block stain; × 325). Note fragmented axons.

F, hypothalamus in a pigeon with chronic thiamine deficiency (Cajal block stain; × 325). Note early changes in small fibers (arrows).

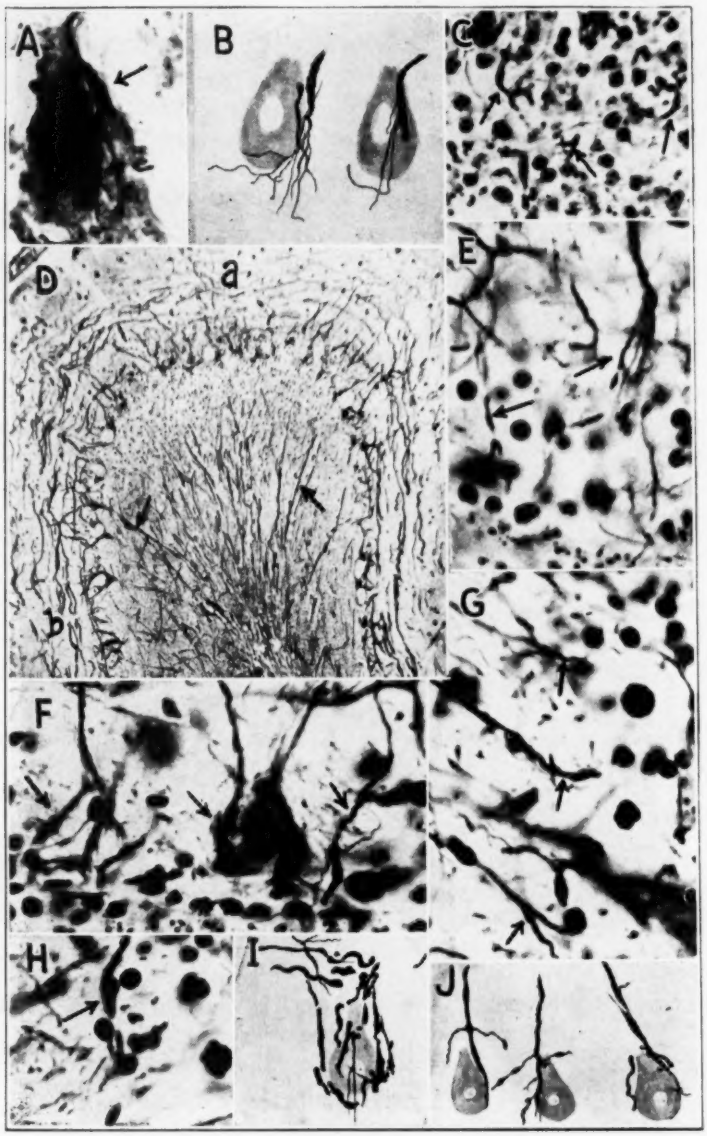

Figure 6

(See legend on opposite page)

than were seen in the acutely deficient pigeons, although the distribution of lesions was the same. The large peripheral proprioceptive nerve fibers, which terminate centrally in the nucleus cuneatus and the nucleus gracilis, as well as other large axons in various parts of the central nervous system, were also found to be degenerating in chronic preparations.

Occasionally, interesting early degenerative changes were seen in small and medium-sized axons of the hypothalamus (fig. 5 *F*) and in the peripheral terminations of the cochlear nerve in the cochlea. Other interesting changes were seen in the striate body, located in the ventrolateral portion of the forebrain, and in the dentate gyrus and the septomesencephalic tract (terminology of Papez). The remaining structures of the forebrain appeared normal.

EXPLANATION OF FIGURE 6

A, Purkinje layer in the cerebellum of a pigeon being restored with thiamine hydrochloride (Cajal frozen section method; × 490). Note swollen stump of basket axon (arrow) and two thin, pale-stained fibers arising from it.

B, drawing to show regenerating fibers (?) arising from the swollen ends of basket axons.

C, granule layer near the apex of a cerebellar convolution in a pigeon with chronic thiamine deficiency (Cajal frozen section method; × 490). Note degenerating moss fibers (arrows).

D, cerebellar convolution in a pigeon with chronic thiamine deficiency (Cajal block stain; × 98). Note the marked decrease in baskets and basket axons at the top of the convolution, near *a*, as compared with the sides of the convolution, near *b*. Purkinje cell axons are also swollen some distance from their cell bodies (arrows).

E, Purkinje cell layer in a pigeon with moderately acute thiamine deficiency (Cajal frozen section method; × 490). Note fragmented basket terminations (arrows); the cytoplasm of the Purkinje cells remains unstained.

F, Purkinje cell layer in a pigeon with moderately acute thiamine deficiency (Cajal frozen section method; × 490). Note degenerating basket terminations and axons (arrows).

G, Purkinje cell layer in a pigeon with chronic thiamine deficiency (Cajal frozen section method; × 490). Note that the baskets have mostly disappeared and the basket axons (arrows) appear abnormal. Here, again, the cytoplasm of the Purkinje cells has not stained.

H, Purkinje cell layer in a pigeon with moderately acute thiamine deficiency (Cajal frozen section method; × 490). Note swollen and fragmented basket termination (arrow).

I, drawing to show fragmented basket terminations as seen in pigeons with acute thiamine deficiency.

J, drawing to show fragmented basket terminations as seen in pigeons with chronic thiamine deficiency. Many fragmented basket terminations have disappeared, and others show early changes.

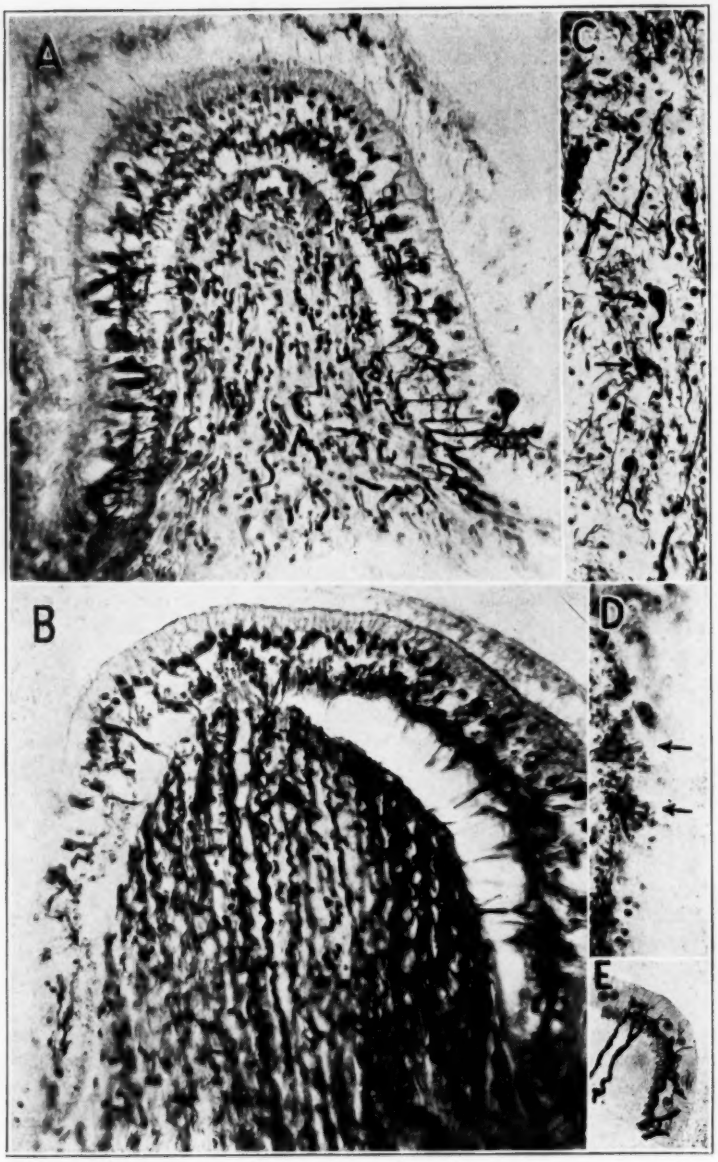

Figure 7

(See legend on opposite page)

Changes in the cell body in the chronically deficient pigeons were as a rule less marked than in the acutely deficient pigeons, although their processes were more extensively affected. For example, the ganglion cells of the nucleus magnocellularis in pigeon 15 exhibited but slight sclerosis, whereas their axons were severely damaged (fig. 4 *C*). The same applies to the very large cells in the reticular formation (fig. 4 *B*). Very few chromatolyzed ganglion cells were seen in Scarpa's ganglion, the nucleus magnocellularis or elsewhere in acute, chronic or repair experiments. Had the experiments been more chronic, or repair been longer, it is expected that many more cells would have exhibited the axon reaction or necrosis.

In 4 chronically deficient pigeons the only observable sign of thiamine deficiency was the cerebellar type of ataxia (staggering without buckling of the knees). Pathologic study of the brains of these birds revealed marked degeneration in the cerebellum, chiefly of the basket and moss fibers, and mild changes in the nucleus magnocellularis and other central terminations of the vestibular nerve. From these and similar observations, we are inclined to believe that the staggering type of ataxia is due to degeneration in the cerebellum.

The nerve endings in the hearts of 4 chronically deficient pigeons with hydropericardium were studied. In no instance were degenerating or even questionably normal fibers seen.

E. Repair Studies.—The fate of neurons the axons of which are degenerating is uncertain. In all probability the badly fragmented ones eventually disappear, but there exists uncertainty with regard to those suffering from early axonal changes. To approach this problem experimentally, a number of very acutely deficient pigeons (similar to pigeons

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EXPLANATION OF FIGURE 7

A, posterior crista from a pigeon with moderately acute thiamine deficiency (Cajal block stain; × 325). Note absence of baskets at the apex of the crista and degeneration of nerve fibers in the upper part of the bony crista. Note also the relatively normal basket terminations to the right of the base of the crista.

B, anterior crista from the pigeon represented in *A* (Cajal block stain; × 325). There are many more normal baskets than in *A*, but even so those at the apex have suffered most. Note that the nerve fibers in the bony crista are more normal than in those shown in *A*.

C, region just rostral to the formation of the posterior commissure (Cajal block stain; × 325). Note the many tortuous and varicosed nerve fibers.

D, anterior crista from a pigeon with chronic thiamine deficiency (Cajal block stain; × 325). Note pale, swollen baskets. These have been retouched to assure their reproduction.

E, drawing to show degenerating basket terminations and axons from which are arising new fibers in a pigeon with chronic thiamine deficiency.

40, 41, 39 and 37) with opisthotonos of short duration were treated for varying periods with frequent large doses of thiamine hydrochloride. Two were killed after one day, 2 others after two days, 2 after four days, 1 after eight days, 1 after nine days and 1 after fourteen days of this treatment. In all the birds opisthotonos was quickly abolished in a few hours and normal behavior maintained by repeated injections of thiamine hydrochloride until the day the animal was killed.

As was pointed out before, the only consistent pathologic changes in very acutely deficient pigeons consisted of swelling, formation of varicosities and neurofibrillar thickening at the axon terminations in the nucleus magnocellularis and, to a less extent, the basket terminations in the cerebellum (table). In the one and the two day repair preparations the axonal changes had not altered. In 1 four day and in the nine day preparations many axons still exhibited early changes and others ventral to the nucleus magnocellularis had fragmented. The other four day and the eight day preparation were free of fragmented axons, but contained a few axons with early changes. In the fourteen day preparation a few axons still exhibited early changes; many others had fragmented. The basket terminations in the cerebellum of these same pigeons displayed similar changes. These observations indicate that many axons with early changes do not continue to degenerate after thiamine is given, but return to normal after a variable period. Others, however, degenerate after a delay of from several days to two weeks.

In other repair studies on pigeons with moderately acute deficiency which characteristically exhibited $++$ and $+++$ degenerative changes in the basket terminations of the cerebellum, somewhat different observations were made. In 1 six and 1 twelve day repair preparation there was an obvious increase in the number of fragmenting baskets. This process of degeneration appeared to have nearly stopped in another twelve and a twenty day repair preparation, as practically no degenerating and only a few normal-appearing baskets were to be found at the tops of the cerebellar convolutions. These observations indicate that most if not all, fragmented basket terminations continue to degenerate and disappear, although, as will be shown now, others may attempt to regenerate.

Regenerating long, thin, coiled fibers, many with terminal knobs, and short thick protoplasmic sprouts with neurofibrillar network were seen arising from the cells of Scarpa's ganglion or their processes in chronically deficient pigeons that were being restored. Similar regenerating sprouts were observed by Cajal[14] in traumatized dorsal ganglia. New and disorganized fibers arising from degenerating stalks were also

14. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, London, Oxford University Press, 1928.

seen in the sensorial epitheliums of the labyrinths (fig. 7 *E*) in pigeons undergoing repair as well as in those with chronic deficiency in which degeneration was progressing elsewhere, i. e., the peripheral nerves and the restiform body.

In the cerebellums of several pigeons receiving thiamine hydrochloride, many very fine, pale-staining twigs arising from swollen and ragged ends of the degenerating basket fibers were identified by means of the Cajal and the Hortega double impregnation method (fig. 6 *A* and *B*). They were tortuous and disorganized, but occasionally one seemed to reach a Purkinje cell. Similar lateral sprouts were observed farther from the fragmented ends of the basket fibers. These new sprouts seemed most numerous after treatment with thiamine for four to eleven days. In 1 twelve day and another twenty day repair preparation they had decreased markedly, a change suggesting that many of them had degenerated. Because of their appearance and origin, we are inclined to believe that these immature-appearing sprouts were new fibers, but their attempt to regenerate seemed to be aborted. We cannot be absolutely certain, however, that they were not resistant fibers or other changes which had gone unrecognized previously.

F. Hemorrhagic Lesions.—Hemorrhages similar to those described recently [15] in thiamine-deficient pigeons were seen in a number of our birds. They were always microscopic and, when present, were surrounded by degenerating axons or damaged ganglion cells. They are believed to be secondary to the parenchymatous changes and will be the subject of a subsequent communication.

COMMENT

In thiamine-deficient pigeons, lateral rotation of the head and opisthotonos were intimately associated with degeneration of the peripheral and central terminations of the vestibular neurons. The degenerative changes in the labyrinths were present in all sensorial epitheliums, but appeared first and were most severe in the posterior cristae. Their physiologic significance will now be discussed.

In pigeons, Ewald,[16] Winkler [10] and the present investigators observed lateral rotation of the head after removal of one labyrinth.

15. Alexander, L.; Pijoan, M.; Myerson, A., and Keane, H. N.: Beriberi and Scurvy: An Experimental Study, Tr. Am. Neurol. A. **64**:135, 1938. Zimmerman, H. M.: The Pathology of the Nervous System in Vitamin Deficiencies, Yale J. Biol. & Med. **12**:21, 1939. Alexander, L.: Wernicke's Disease: Identity of Lesions Produced Experimentally by B_1 Avitaminosis in Pigeons with Hemorrhagic Polioencephalitis Occurring in Chronic Alcoholism in Man, Am. J. Path. **16**:61, 1940.

16. Ewald, J. R.: Physiologische Untersuchungen über das Endorgan des Nervus octavus, Wiesbaden, J. F. Bergmann, 1892; cited by Winkler.[10]

This seems to have been due chiefly to destruction of the utricle on the side to which the animal's occiput was turned.[17] Except that rotation was more marked and of longer duration in the operative experiments, it was similar to that observed in pigeons with thiamine deficiency. In frogs, McNally and Tait selectively severed the nerve supply to the different semicircular canals of either or both labyrinths and observed the posture of these animals, both while resting and after they were stimulated by motion.[18] After section of the nerves to both posterior cristae their frogs had a tendency to stand with their heads and forelegs extended, and when they were stimulated by movement, this position became exaggerated and the animals fell over backward. When the nerves to both anterior cristae were sectioned there was a tendency for the frogs to assume a flexed posture, with head low and forelegs flexed. These experiments were interpreted to indicate that the two anterior cristae act together to increase the tonus of the extensor muscles of the head, neck and both forelegs and the two posterior cristae counteract this by increasing the flexor tonus. Normally the two pairs of cristae balance one another. The utricles help the cristae check body movements in their direction, and to a certain extent compensate for their loss.[19] Consequently, when denervation of the utricles was added to denervation of any or all of the cristae, abnormal or unchecked movements were greatly increased. Assuming that the fundamental functions of the labyrinth throughout the vertebrate phyla are the same, it should still be remembered that anatomic differences probably influence the responses which occur after labyrinthine stimulation in the different species; for example, the very long neck of the pigeon accounts for the conspicuous nature of opisthotonos in this animal.

This gives us a relatively simple explanation, based on the distribution of degeneration in the peripheral vestibular nerves, for lateral rotation and opisthotonos in thiamine deficiency. Physiologic and pathologic changes probably appear first and are most severe in neurons the peripheral processes of which terminate in the posterior crista. This distribution of degeneration may be determined by the relative length of the vestibular nerve fibers to the different sensorial epitheliums, those to

17. (*a*) Versteegh, C.: Ergebnisse partieller Labyrinth—Extirpation bei Kaninchen, Acta oto-laryng. **11**:393, 1927. (*b*) McNally, W. J.: Experiments Demonstrating the Interaction of the Semicircular Canals and the Utricles, Tr. Am. Acad. Ophth. **38**:265, 1933. (*c*) Tait, J., and McNally, W. J.: Some Features of the Action of the Utricular Maculae of the Frog, Phil. Tr. Roy. Soc., London, s.B **224**:241, 1934.

18. McNally, W. J., and Tait, J.: Ablation Experiments on the Labyrinths of the Frog, Am. J. Physiol. **75**:155, 1925; Some Results of Section of Particular Nerve Branches to the Ampullae of the Four Vertical Semicircular Canals of the Frog, Quart. J. Exper. Physiol. **23**:147, 1933.

19. McNally.[17b] Tait and McNally.[17c]

the posterior crista being the longest in the labyrinth. However, in the quiet animal, or because of other compensatory mechanisms, i. e., the utricles, these pathologic changes do not manifest themselves physiologically. Soon function becomes impaired in the utricles, and, by chance, one utricle may become affected before the other. This produces forceful lateral rotation of the occiput toward the side of greatest impairment. In other instances the changes in the utricle are bilaterally uniform, and then lateral rotation is absent. As impaired function increases in the posterior crista and becomes bilateral in the utricle the position of opisthotonos appears.

Enopisthotonos (1) was frequently preceded by opisthotonos, (2) appeared in pigeons with the most severe deficiency and (3) was often converted to opisthotonos by an injection of thiamine hydrochloride. These facts suggest that this posture was the result of continued functional and degenerative changes in the labyrinths, eventuating in greater but more uniform impairment of function than was sustained by pigeons with opisthotonos. This thesis is supported by the observations of Ewald [16] and Winkler [19] that destruction of both labyrinths produces an atonic flexed position of the head and neck in normal pigeons. Unfortunately, histologic support for this was not available because the incidence of enopisthotonos was very low in this series of experiments.

Degeneration was present in vestibular nerve fibers to all points of central termination, but appeared first and was most marked in the endings to the lateral part of the nucleus magnocellularis. The significance of these changes is obscure, as very little is known about the functions of the vestibular nuclei. Decerebration produces the condition of extensor rigidity in most animals. Roughly, this consists of extensor rigidity of the extremities, most marked in the forelegs, and extension of the tail, back, neck and head. In pigeons, decerebration by section through the midbrain is accompanied by marked opisthotonos, and sometimes backward rolling, which is very similar to opisthotonos as seen in thiamine-deficient pigeons. It is thought that the vestibular nuclei are directly concerned with the surgical production of extensor phenomena, since section just above them gives a maximum degree of rigidity [20] and section below or their destruction [21] abolishes this state. Selective destruction of Deiters' nucleus and the descending vestibular

20. Magnus, R.: Welche Teile des Zentralnervensystems müssen für das Zustandkommen der tonischen Hals- und Labyrinthreflexe auf die Körpermuskulatur vorhanden sein? Arch. f. d. ges. Physiol. **159**:224, 1914. Bazett, H. C., and Penfield, W. G.: A Study of the Sherrington Decerebrate Animal in the Chronic as Well as the Acute Condition, Brain **45**:185, 1922.

21. Fulton, J. F.; Liddell, E. G. T., and Rioch, D. McK.: The Influence of Unilateral Destruction of the Vestibular Nuclei upon Posture and the Knee Jerk, Brain **53**:327, 1930.

nuclei on one side in guinea pigs has been shown by Buchanan [22] to produce circular walking to the same side. Circular walking to the opposite side resulted when the medial vestibular nucleus, the medial reticular formation and the medial longitudinal fasciculus were destroyed. Forced rolling was produced in cats by unilateral lesions in the vestibular nuclei.[21]

These experiments indicate the importance of the central connections and nuclei of the vestibular nerve but fail to indicate specific centers which may be involved in the production of opisthotonos or lateral rotation of the head. Even more conjectural is the significance of the changes which were observed in the secondary vestibulocochlear centers and their projection fibers, the trapezoid body. Degeneration in the cochlea of chronically deficient pigeons presumably was accompanied by impairment of hearing.

Although axons (also dendrites) in thiamine-deficient pigeons degenerate first at a point most distant from their trophic cell bodies, it should not be supposed that the deficiency is so confined. Most likely the entire neuron suffers, degeneration appearing where it does because of the difficulty, under the circumstances, with which this part of the neuron is maintained in a normal metabolic state. If the central and peripheral terminations of a vestibular neuron degenerate simultaneously, it would be justifiable to suggest that fibers arising in the posterior crista terminate in the lateral part of the nucleus magnocellularis, because of the predominance of degeneration in these two places. On the other hand, one cannot dismiss from consideration the possibility that degeneration in one process (central or peripheral) spares the other. In this case it would be equally justifiable to suggest that nerve fibers to the lateral part of the nucleus magnocellularis arise from the utricle, since both forced lateral rotation of the head and degeneration in the nucleus magnocellularis occur early, degeneration centrally sparing the peripheral nerve endings. Regardless of the type of degeneration which occurs, impaired function of the neuron results. Judging from our pathologic studies, the nucleus magnocellularis would seem to be of considerable importance in the production of the neurologic symptoms of acute avian thiamine deficiency.

In a previous communication [1a] it was suggested that the "opisthotonos of thiamine deficiency is a manifestation of decerebration due to a functional impairment of the neurons which have an inhibitory influence upon the lower brain stem centers." This was based on the similarity of opisthotonos to decerebrate extensor rigidity in pigeons In the light of the present experiments we modify this statement. Opisthotonos in thiamine-deficient pigeons is probably due to a selec-

22. Buchanan, A. R.: Circling in Guinea Pigs with Lesions in the Brain Stem, Proc. Soc. Exper. Biol. & Med. **45**:389, 1940.

tive or partial release of the central vestibular centers from labyrinthine control, although release from higher centers may also be a factor. It is of considerable interest that surgical release of the central vestibular centers from upper brain stem control results in a condition very similar to that produced by release of these same centers from partial labyrinthine control as a result of thiamine deficiency. It is not to be assumed, however, that this proves the two conditions to be identical, although it suggests that the causal mechanisms are very similar. The present study confirms a previous conclusion [1a] that functional impairment of neurons is sufficient to produce this release. As all neurons are rarely affected by the deficiency simultaneously, however, many will degenerate while others remain normal histologically.

In a significant physiologic study of thiamine deficiency in rats, Church [23] described four successive stages in the development of neuromuscular symptoms. Generalized hypotonia usually appeared first and lasted one to two days. This was followed by generalized muscular incoordination or ataxia of about two to three days' duration. Disturbances of equilibrium then occurred, during which normal posture was regained with difficulty, and spontaneous nystagmus occasionally developed. In some animals a hyperexcitable stage followed, which consisted of violent struggling when normal posture was lost. During the last two stages, an occasional animal displayed marked hypertonicity with extension of the antigravity muscles, retraction of the neck, arching of the back and elevation of the tail. Such animals resembled decerebrate preparations to the extent that they exhibited the crossed extensor reflex.

After disturbances in equilibrium had developed, Church's animals were unable to exhibit the labyrinthine righting reflex, but neck and body righting reflexes were unimpaired. Vestibular function was shown to be impaired also by a standard rotation test, which produced prolonged nystagmus in the deficient rats. The peripheral proprioceptive mechanisms were thought to be intact, as stretching muscles or tendons produced afferent peripheral nerve impulses in thiamine-deficient rats which, when recorded by the oscillograph, were similar to those seen in normal rats. This was interpreted to indicate that the ataxia was central in origin. In commenting, Church suggested that the neurologic symptoms of vitamin B_1 deficiency in the rat could be explained by loss of proprioceptive control due chiefly to lesions in the vestibular nuclei. He observed perivascular hemorrhages in the region of these nuclei which he regarded as secondary to tissue changes resulting from the specific lack of vitamin B_1.

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23. Church, C. F.: Functional Studies of the Nervous System in Experimental Beriberi, Am. J. Physiol. **111**:660, 1935.

In the main, these results confirm our histologic and clinical observations. The relative infrequency of extensor rigidity in his rats may have been due to the fact that they fed voluntarily and consequently, as he pointed out, became very emaciated. It is known from previous studies on pigeons [1b] that this makes a deficient state more chronic, in this way decreasing the incidence of opisthotonos. Actually, the deficiency in his rats was probably intermediate between the acute and the chronic phase in our pigeons, a stage which we should consider subacute. The ataxia which he observed and demonstrated experimentally not to be caused by degenerating peripheral nerve fibers was probably due to cerebellar as well as vestibular lesions, as the chronicity of his experiments was insufficient to produce marked degeneration of peripheral proprioceptive nerve fibers.

The cerebellar type of ataxia, characterized by staggering, was seen in both the acute and the chronic preparations. In these animals lesions were observed chiefly in two cerebellar systems: (1) the basket fibers, which suffered the first and most severe changes, and (2) the spinocerebellar and moss fibers, and to a lesser extent the granule fibers. This classification of the degenerating cerebellar fibers is based on the suggestions of Cajal that the spinocerebellar fibers terminate as moss fibers and the granule fibers form an anatomic link between the moss fibers and the dendrites of the Purkinje cells. If the climbing fibers are terminations of the spinocerebellar fibers, as Bárány [24] contended, many degenerating climbing fibers should have been observed in chronic preparations in which the spinocerebellar tracts suffered great damage. Such was not the case in our experiments. It appears that ataxia can be produced in thiamine-deficient pigeons by a combined degeneration of coordinating and afferent systems of the cerebellum. The efferent Purkinje cells and their axons remained normal in most instances, but in a few very chronic experiments the Purkinje axons showed marked early and a few late changes. One can only wonder if degeneration of the basket or moss fibers alone would have produced ataxia, or if one system is capable of compensating for damage to the other. Degeneration of basket fibers has been observed in human beings in whom typical cerebellar symptoms were apparently absent.[25] Ataxia was present in human beings in whom the Purkinje cells were degenerated,

24. Bárány, R.: Beziehungen zwischen Bau und Funktion des Kleinhirns nach Untersuchungen am Menschen. Vortrag gehalten in der morphologisch-physiologischen Gesellschaft, Wien, December 1911, Wien. klin. Wchnschr. **25**:1737, 1912; Die Bedeutung der Assoziationzellen im Kleinhirn, Internat. Zentralbl. f. Ohrenh. **14**:161, 1916.

25. Ramón y Cajal, S.: Sur quelques lésions du cervelet dans un cas de démence précoce, Trab. d. Lab. de invest. biol. de la Univ. de Madrid **24**:181, 1926.

leaving for the most part the other elements of the cerebellum intact.[26] The clinical significance of degeneration of the central connections of the vestibular nerves to the cerebellum in our thiamine-deficient pigeons is not clear. Possibly it contributed to the ataxia which preceded and followed opisthotonos.

Whereas degeneration appeared in the central terminations of the optic nerve fibers and in secondary optic centers in both the acute and the chronically deficient pigeons, the oculomotor and trochlear nerves and their nuclei did not become significantly affected except in the chronic preparations. Usually degeneration was then already marked throughout the rest of the proprioceptive system.

The previous [1a] and the present study have shown that the predominating pathologic changes in thiamine-deficient pigeons can be varied considerably by altering the speed of thiamine depletion. In birds made acutely deficient the vestibular system suffered the first and most severe degeneration. This was followed closely by degeneration in the cerebellum and, in some cases, the optic lobes. In very chronic preparations, degeneration of peripheral proprioceptive nerve fibers appeared first and sometimes became marked before changes appeared elsewhere. Later, lesions in the cerebellum, vestibular system and optic lobes developed, the severity of changes in each system varying but conforming roughly to the order named. The oculomotor and trochlear nerves and their nuclei degenerated later. In cases of intermediate (subacute) deficiency the pathologic course was less distinctive. Degeneration of the cerebellar systems and spinocerebellar tracts was frequently the more marked. Changes in the vestibular system were present but not so prominent, and the optic system was affected to a variable degree. The sequence of events which have been seen in the more chronically thiamine-deficient pigeons conforms in a general way to the progression of neurologic manifestations in several alcoholic patients.[27] Ataxia and weakness of the extremities were followed by ophthalmoplegia, and regression of symptoms in reverse order occurred when vitamins were given. This agrees essentially with the statement of Jolliffe, Wortis and Fein [28] that ophthalmoplegia is invariably preceded or accompanied by peripheral neuropathy in thiamine-deficient patients.

In a previous study [1a] it was shown that the large and long nerve fibers were more sensitive to lack of thiamine than the smaller and shorter fibers. To a certain extent this variable resistance to degen-

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26. Holmes, G.: A Form of Familial Degeneration of the Cerebellum, Brain **30**:466, 1907. Parker, H. L., and Kernohan, J. W.: Parenchymatous Cortical Cerebellar Atrophy (Chronic Atrophy of Purkinje's Cells), ibid. **56**:191, 1933.

27. These patients were observed at the Montreal Neurological Institute.

28. Jolliffe, N.; Wortis, H., and Fein, H. D.: The Wernicke Syndrome, J. Nerv. & Ment. Dis. **93**:214, 1941.

eration determines where the neuronal lesions will appear first and where they will be the most severe. When the deficiency develops quickly the large vestibular and peripheral proprioceptive nerve fibers probably become impaired almost simultaneously. However, "locomotor ataxia" cannot be demonstrated because of the presence of opisthotonos. When thiamine is administered both sets of fibers and the clinical behavior return to normal quickly. When the deficiency develops slowly the nervous system is depleted of this substance gradually. Slight differences in the sensitivity of the large fibers to thiamine lack then become manifest. Probably because of their much greater length, and hence greater energy requirement, the proprioceptive nerve fibers in the peripheral nerves degenerate first and "locomotor ataxia" develops. Later, and as a terminal event, vestibular nerve fibers may degenerate and opisthotonos (or enopisthotonos) results.

Degenerating axons in the central nervous systems of thiamine-deficient pigeons may be conveniently divided into two groups: those which continue to degenerate after thiamine is given and those which are restored to normal by the giving of thiamine. Probably most fragmented axons eventually degenerated and their cell bodies disappeared. The speed of recovery from opisthotonos, however, indicates that many others with impaired function must have been restored to normal. As many axons to the nucleus magnocellularis were histologically altered in pigeons having moderately acute deficiency with opisthotonos, yet few seemed to have disappeared in similar pigeons which had been rehabilitated clinically by administration of thiamine, it is not unlikely that many functionally impaired axons exhibited early histologic changes which were capable of being restored to normal appearance by thiamine. Some of these may have degenerated later and have constituted the fragmented axons near the nucleus magnocellularis which were present after fourteen days of thiamine treatment. The degree of abnormality in the trophic cell bodies may have determined which ones were capable of being repaired. In extremely acute preparations the anatomic changes are so far behind the biochemical ones that this rule probably does not apply.

Cajal[14] observed regenerating fibers arising from dendrites of Purkinje cells both in a case of traumatization of the cerebellum and in a case of dementia praecox with uremic poisoning,[25] and Rossi[29] observed similar sprouts arising from degenerating axons of Purkinje cells in man. In the present investigations, disorganized pale-staining, thin fibers and protoplasmic sprouts were seen arising from degenerating axons of basket fibers in pigeons which were being restored to normal

29. Rossi, U.: Per la rigenerazione dei neuroni, Trab. d. Lab. de invest. biol. **6**:227, 1908.

from a state of thiamine deficiency. Although many of these fibers eventually disappeared and the damaged axons degenerated, the attempts of the fragmented axons to regenerate were vigorous and suggested that synapses might be readily restored to normal. If so, a relatively simple explanation is available for the clinical phenomena and, as well, the absence of histologic lesions in acutely deficient pigeons. Certainly, the conditions for regeneration in thiamine deficiency are ideal, as distortion of axons and nerve endings, which results from trauma, is absent. The remissions which occur in certain degenerative diseases of the central nervous system in human beings could be explained by the same mechanism. Exacerbations would be accompanied by degeneration of synapses or by impaired function of neurons with early degenerative changes in the periphery of their axons. The number of synapses to regenerate or of axons to be restored to normal would then determine the extent of rehabilitation during remissions. The long period necessary for many of the altered axons in very acutely deficient pigeons to return to normal histologically suggests that anatomic repair was mediated through an outgrowth of axonal material from the more normal part of the neuron, much as axons regenerate in peripheral nerves.

In a recent review, Meiklejohn [30] concluded that the polyneuritis associated with alcoholism, pregnancy and gastrointestinal disturbances had not been conclusively related to thiamine deficiency and that there was as yet no clear experimental evidence showing that true anatomic polyneuritis in animals is curable by thiamine. As a criterion he suggested that "certain proof that thiamin will cure polyneuritis can only be achieved by a carefully controlled study in which all other factors of the vitamin B complex are excluded from the diet and thiamin alone is administered." In previous experiments which were reported while Meiklejohn's paper was in the process of publication this criterion was satisfied. Thiamine-deficient pigeons with ataxia and leg weakness were restored to normal in from one to seven weeks by tube feeding them diet II (a highly purified diet containing none of the B group of vitamins) plus thiamine hydrochloride, the clinical improvement being paralleled by a numerical increase of myelinated nerve fibers in the peripheral nerves. In a subsequent publication [1b] these experiments were reaffirmed, and in the present study the results were confirmed and supported by the observation of regeneration in cranial nerves. In both studies similar birds were restored on a diet containing autoclaved yeast (diet III) plus thiamine hydrochloride, and for convenience many others were given normal grain. Regardless of which of these diets was employed the clinical and histologic observations were identical. Meiklejohn's refer-

30. Meiklejohn, A. P.: Is Thiamin the Antineuritic Vitamin? New England J. Med. **223**:265, 1940.

ences to vomiting are not applicable to these experiments since (1) very few chronically deficient pigeons with ataxia and leg weakness vomited and (2) since the B complex group of vitamins was absent from the diet of many pigeons during both thiamine depletion and repair. We agree that the term "polyneuritis" is a poor one, but for different reasons; no evidences of inflammation are present, the changes being strictly degenerative.

SUMMARY AND CONCLUSIONS

Using dietary methods described before[1a] and staining methods which demonstrate the neurofibrillar structure of the neuron, the following observations were confirmed: (1) the first neuronal histologic change in thiamine-deficient pigeons is degeneration of the distal part of the axon, and changes in myelin are secondary to this; (2) degeneration proceeds centralward and is accompanied by slight shrinkage or sclerosis of the cell body; (3) the large nerve fibers degenerate first and the medium later, the small fibers usually remaining intact, and (4) opisthotonos may not be attended by any definite neurologic lesions. In the present study the early axonal changes were shown to consist of thickening of the neurofibrils and generalized swelling, followed by the formation of varicosities, in the distal parts of cell processes. This is followed by fragmentation.

Closer study of opisthotonos in acutely deficient birds revealed that it may be preceded by lateral rotation of the head similar to that which results when one labyrinth (utricle) is destroyed in a normal bird. This is succeeded by phasic extension of the neck and then the head. This may be accompanied by very slight or no degenerative changes in the vestibular system or elsewhere in very acutely deficient birds, but in pigeons with moderately acute deficiency degeneration occurs in the sensorial epitheliums of the labyrinth, especially of the posterior crista, and in the central endings of the vestibular nerve fibers, especially in the lateral part of the nucleus magnocellularis. It is concluded that opisthotonos is due to a selective release of the central vestibular centers from labyrinthine control. Because of its clinical characteristics enopisthotonos is thought to be due to still further impairment of the vestibular nerves.

In chronically deficient pigeons without opisthotonos all central and peripheral terminations of the vestibular nerves are moderately degenerated; no preponderant site of degeneration is present.

In both acutely and chronically deficient pigeons many basket terminations and moss fibers in the cerebellum degenerated, and in several mildly chronic (subacute) preparations this was associated with staggering (cerebellar ataxia). This is quite distinct from "locomotor ataxia," which occurs in very chronic experiments as the result of degeneration of the very large proprioceptive nerve fibers in the peripheral

nerves.[1a] Also, in both acute and chronic experiments inconsistent degeneration was present in the optic lobes, the nucleus rotundus of the thalamus, the reticular formation and the secondary vestibulocochlear centers, and in chronic experiments, in the cell bodies and peripheral nerves of the third and fourth cranial nerves and elsewhere.

The following generalization may be made: The neurologic manifestations of an acute or a chronic deficiency in thiamine are accompanied first by impaired function and then by degeneration of the primary neurons of the proprioceptive nervous system and the central terminations of the optic nerves. Changes occur next in internuncial neurons of these same systems. Finally, after prolongation of the deficiency, the efferent nervous system becomes affected.

On the basis of curative experiments, neurons affected histologically by thiamine lack were divided into those which (1) return to normal when thiamine is given and (2) those which continue to degenerate. It appeared that many of those suffering from early degenerative changes belong definitely to the first group. Although fibers which had fragmented probably continue to degenerate, evidences of regeneration were seen in the cerebellar basket terminations.

Present observations indicate that brain hemorrhages in our thiamine-deficient pigeons were secondary to changes in the axons and cell bodies. These hemorrhages appear to have no relation to the clinical behavior.

AMYLOID NEURITIS

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While deposits of amyloid may accumulate in quantities sufficient to interfere with the function of some organs, such as the kidneys and the liver, the nervous system remains singularly spared of such encroachment. The reason for this is not obvious. In any event, the damage caused by amyloid, wherever it appears, seems to be the result of compression or of arterial obliteration. A few cases have been reported in which the brain was invaded. It should be noted that corpora amylacea and amyloid are unrelated substances. Small amounts of amyloid have been described in the large vessels of the base of the brain and their branches.

Fischer and Holfelder [1] reported the case of a man aged 45 who in 1921 had been given extensive irradiation for a squamous cell carcinoma situated in the right temporal area. This treatment having failed, the area was excised in 1923. In 1929 a sensorimotor disability appeared in the left arm and leg. Exploration of the corresponding area of the brain revealed edema, and biopsy disclosed perivascular and intracerebral deposits of amyloid. The patient was followed for six months, during which time he appeared to have recovered. Fischer and Holfelder attributed the deposits of amyloid to a reaction to the irradiation.

Saltykow [2] examined a brain that had been sent to him from an asylum. In the cortex and white matter he found three adjoining nodules, the size of hazelnuts, that grossly resembled areas of gliosis. These proved to be amyloid; they stained with methyl violet and contained nerve and glia cells.

Morgenstern [3] referred to a case of jacksonian epilepsy due to a cerebral amyloid tumor which had been reported by Schwarz in 1930.

From the Section on Neuropathology (Dr. Kernohan) and the Section on Clinical Neurology (Dr. Woltman) of the Mayo Clinic.

1. Fischer, A. W., and Holfelder, H.: Lokales Amyloid im Gehirn; eine Spätfolge von Röntgenbestrahlungen, Deutsche Ztschr. f. Chir. **227**:475-483, 1930.

2. Saltykow, S.: Zur Frage des lokalen Amyloids der Hirngefässe, Virchows Arch. f. path. Anat. **295**:590, 1935.

3. Morgenstern, Z. I.: Ein Fall von lokalem Amyloid der Hirngefässe, Virchows Arch. f. path. Anat. **294**:334-339, 1935.

Morgenstern described the case of a woman aged 22 who had had jacksonian attacks that began in the left foot. There were left hemiparesis and astereognosis, headache, choked disks and roentgenologic evidence of increased intracranial pressure and thickening of bone in the right parietal area. A presumptive diagnosis of meningioma was made. On exploration, a large, nodular sarcoma was found, around which were blood vessels containing amyloid. The material stained with congo red, but the iodine–sulfuric acid and methyl violet tests gave negative results. The more distant vessels were free of amyloid.

Bürgi,[4] in writing of amyloid tumors of bone, stated that they may occur in the skull and in the spine. He reported the case of a veterinarian aged 51 in whom there developed a post-traumatic, brain-compressing amyloid tumor of the parietal bone, insensitive to roentgen therapy. The roentgenograms disclosed a large mottled tumor, which, Bürgi said, could be classified only by biopsy.

The demonstration of amyloid in nerves and their ganglia, especially in the blood vessels accompanying these structures, has been reported more often. Lubrinoff (cited by Wichmann [5]) found amyloid in the vessels of the sympathetic ganglia. Wichmann and Schmorl (cited by Belokrenitzky [6]) demonstrated it in the solar plexus and in the interstitial structures of the sciatic nerve, Schilder,[7] in the vessels of cutaneous nerves, Belokrenitzky, in the sciatic, crural, pneumogastric and cardiac and renal nerves; Askanazy,[8] in nerves of the breast; Königstein,[9] in the pelvic nerves; Lubarsch,[10] in the pericardial nerves, and Mollow and Lebell,[11] in the splanchnic plexus, the choroid plexus and the hypophysis. Most authors have emphasized that when amyloid is found, it lies in the vessels or supportive tissue and not in the parenchymal tissue itself and that it does not cause degeneration of the nerve fibers.

4. Bürgi, U.: Ueber einen Fall von solitärem Amyloidtumor des Scheitelbeins, Frankfurt. Ztschr. f. Path. **50**:410-428, 1937.

5. Wichmann, G.: Die Amyloiderkrankung, Beitr. z. path. Anat. u. z. allg. Path. **13**:487-628, 1893.

6. Belokrenitzky, S.: De la dégénérescence amyloïde des nerfs, Thesis, Geneva, 1911.

7. Schilder, P.: Ueber die amyloide Entartung der Haut, Frankfurt. Ztschr. f. Path. **3**:782-794, 1909.

8. Askanazy, M.: Ueber Amyloid in der Mamma und die Abhängigkeit der Amyloidablagerung von der Organfunktion, Beitr. z. path. Anat. u. z. allg. Path. **71**:583-594, 1923.

9. Königstein, H., and Spiegel, E. A.: Muskelatrophie bei Amyloidose, Ztschr. f. d. ges. Neurol. u. Psychiat. **88**:220-225, 1924.

10. Lubarsch, O.: Zur Kenntnis ungewöhnlicher Amyloidablagerungen, Virchows Arch. f. path. Anat. **271**:867-889, 1929.

11. Mollow, W., and Lebell: Zur Klinik der systematisierten Amyloidablagerung, Wien. Arch. f. inn. Med. **22**:205-228, 1932.

In the case reported by De Navasquez and Treble,[12] however, the neurologic changes were attributed to the presence of amyloid. The general picture suggested beriberi. The patient was a man aged 36 who had had diarrhea for two years. The tongue was smooth but not sore, and the filiform papillae were atrophic. The pupils were small; they did not react to light and responded only sluggishly on convergence. There were general muscular wasting and great weakness, especially of the hands. The patellar and achilles tendon reflexes were absent. Sensation, including appreciation of vibration, was normal. There was achylia; the Wassermann reaction of the blood was negative; the concentration of hemoglobin was 82 per cent; erythrocytes numbered 4,100,000 and leukocytes 12,900 in each cubic millimeter of blood; the percentage of reticulocytes was 4.5; the spinal fluid gave a positive Pandy reaction; the colloidal gold curve was 2443333200, and the protein content was 160 mg. per hundred cubic centimeters. The urine contained albumin and some erythrocytes. The concentration of vitamin B_1 was within normal limits and the output of ascorbic acid 3 mg. per day. One hundred milligrams of thiamine hydrochloride was given daily by intravenous injection. A hemolytic streptococcic infection of the throat and cardiac failure caused the patient's death, seven weeks after his admission.

Amyloid was found in all tissues except the brain and the spinal cord. The dorsal root and sympathetic ganglia and the right ulnar, peroneal and sciatic nerves were greatly enlarged by the accumulation of amyloid in the vessel walls and connective tissue. The amyloid was distributed around fibers and nerve cells, causing distortion of the cells and compression of the fibers.

De Navasquez and Treble referred to other cases described in the literature which, in their opinion, bore a similarity to their own case. One of these was a case reported by De Bruyn and Stern[13] as an instance of hypertrophic polyneuritis of Dejerine and Sottas.

Königstein and Spiegel[9] and Königstein[14] reported the case of a man aged 60 in whom dysphagia and wasting of the muscles of the hands appeared after an attack of erysipelas. In the central nervous system and pia and the related vessels no amyloid was found, but in the peripheral nerves amyloid was seen in the epineurium and vessels. This was present in large amounts in the nerves of the pelvis, but no nerve fibers seemed to have been damaged by it. The muscles also contained much

12. De Navasquez, S., and Treble, H. A.: A Case of Primary Generalized Amyloid Disease with Involvement of the Nerves, Brain **61**:116-128 (March) 1938.

13. De Bruyn, R. S., and Stern, R. O.: A Case of the Progressive Hypertrophic Polyneuritis of Dejerine and Sottas, with Pathological Examination, Brain **52**:84-107 (April) 1929.

14. Königstein, H.: Ueber Amyloidose der Haut, Arch. f. Dermat. u. Syph. **148**:330-383, 1925.

amyloid, and the authors contended that this, and not the involvement of the nerves, accounted for the muscular weakness.

Lubarsch was led to the same conclusion in the case of a man aged 53, in whom there had developed progressive rigidity with a picture resembling scleroderma with involvement of the muscles. A presumed carcinoma of the tongue proved to be an amyloid tumor. The vessels and the connective tissue of the muscles contained amyloid, but the brain, cord, peripheral nerves and ganglia were free from it, with the exception of small amounts of amyloid in the arterioles of the pericardial nerves; the nerve fibers themselves were free.

REPORT OF A CASE

We should like to report the case of a man aged 50 who was observed from July 25 to July 31, 1932.

History.—The patient gave as his chief complaint pain and weakness in the extremities. Two or three years before it had been observed that the patient became unusually drowsy and sometimes fell asleep while talking to business associates. Seventeen months before admission there had been some swelling of the submental glands, malaise and difficulty in swallowing. In the spring of 1931 he complained of weakness in the lower extremities, and in climbing stairs helped to pull himself up by placing his hand on the banisters. In May 1931 tonsillectomy was performed and the sinuses were treated, without material improvement. For two days there was diplopia. In August some swelling and tingling of the right leg occurred. The patient was treated for a disorder of the kidneys, and the swelling disappeared. In April 1932 he had had cramping abdominal pains for two weeks and diarrhea and headache for a few days. Constant, aching, flashing and burning pain and weakness appeared in the lower extremities. In June, one month before coming to the clinic, tingling also appeared in the hands. After treatment with a high vitamin diet, the tingling in the hands and legs lessened; however, a leathery sensation remained in the legs. The pain continued, and the extremities were so sensitive that the patient could not endure contact with the bed clothing. Occasionally there was slight fever. The legs had become so weak that he could hardly move them in the bed. A diagnosis of multiple neuritis was made. Examination of the spinal fluid was said to have given negative results.

Examination.—Examination of the eyegrounds and ocular movements gave normal results. There was weakness of moderate degree of both hands, of the lower extremities and of the muscles of the left side of the face, particularly about the mouth. Occasional fibrillary twitchings were noted in the upper extremities. Marked hyperesthesia of the lower extremities was present, and the nerve trunks and muscles were very tender. The skin of the hands and feet presented a somewhat atrophic appearance. The patellar and achilles tendon reflexes were absent and the plantar responses were flexor. A diagnosis was made of polyneuritis with facial palsy.

The skin was dry. The axillary lymph nodes were somewhat enlarged. The blood pressure measured 112 mm. of mercury systolic and 70 mm. diastolic. The temperature was normal. Urinalysis gave normal results. The concentration of urea in the blood was 36 mg. per hundred cubic centimeters. The concentration of sugar was 97 mg. per hundred cubic centimeters of blood, and that of protein was 5.53 Gm. per hundred cubic centimeters of serum. Blood counts and differential counts gave normal results. Examination of a smear of the blood showed

slight toxic changes. On June 29 some purpuric spots had been noted about the face and neck. There were 224,000 platelets per cubic millimeter of blood. The bleeding time was two minutes. The concentration of fibrinogen was 320 mg. per hundred cubic centimeters of plasma. The plasma coagulation index was 0.66, the normal value being 1.0. Analysis of the urine for lead, arsenic and thallium gave negative results. On July 31 the patient became nauseated and drank some water, and respiration stopped abruptly.

Necropsy.—No obvious lesions were found to explain satisfactorily the cause of death. However, there were several discrepancies in our observations, the most important being the degree of sclerosis of the coronary arteries and the condition of the myocardium. The sclerosis of the coronary arteries was graded 1 on a basis of 1 to 4, in which 1 indicates the least and 4 the greatest degree of sclerosis. This minor degree of sclerosis persisted even down to the smallest branches visible to the naked eye; yet there were small foci of fibrosis simulating chronic infarctions of the myocardium. It was only on microscopic examination of portions of the various organs that the true nature of the disease process was discovered.

All tissues were stained by the various technics recommended for the demonstration of amyloid in tissues, such as the congo red, the methyl violet and the iodine–sulfuric acid method.

There was amyloid in the wall of almost every small artery and arteriole and of some capillaries of every organ of the chest, abdomen, pelvis and neck. The amyloid was limited for the most part to the media of the small arteries and arterioles; the endothelium of the intima was usually intact, and no amyloid was present in the parenchyma of any of the organs. The smooth muscle of the media of these vessels had been replaced by the amyloid, which was so abundant as to narrow the lumen greatly and in some places almost to occlude it. In some of the small arteries the masses of amyloid had passed into and through the adventitia. Where the amyloid nodules had entered the surrounding connective tissue there frequently were large, multinucleated foreign body giant cells. We were unable to find amyloid in any connective tissue, aside from those small masses which had passed beyond the adventitia of the blood vessels.

In the skeletal muscles changes similar to those observed in the internal organs were found. The media of almost all the middle-sized and small arteries and the arterioles was replaced by amyloid. In some, the lumen was narrowed, and the amyloid had passed through the adventitia into the surrounding connective tissue. About 1 per cent of the muscle fibers contained amyloid. The muscle fibers of the diaphragm, on the other hand, were much more involved by the amyloidosis. Approximately 10 per cent of the muscle fibers were replaced wholly or partially by amyloid. The myocardium, on the other hand, did not contain any amyloid, but did show some replacement fibrosis. The larger vessels were normal, but on microscopic examination the media of the smaller branches of the coronary arteries and the arterioles was replaced extensively by the amyloid. In many instances the amyloidosis of the media was so extensive as to occlude completely, or almost completely, the lumen of the vessel. These occlusions undoubtedly had produced the extensive fibrosis which was seen at necropsy and on microscopic examination. The amyloidosis had spread also into the adventitia of the blood vessels and into the surrounding connective tissue but had not replaced any of the muscle spindles themselves. The smooth muscle of the gastrointestinal tract was not included in the amyloidosis, although the small arteries and arterioles were degenerated extensively.

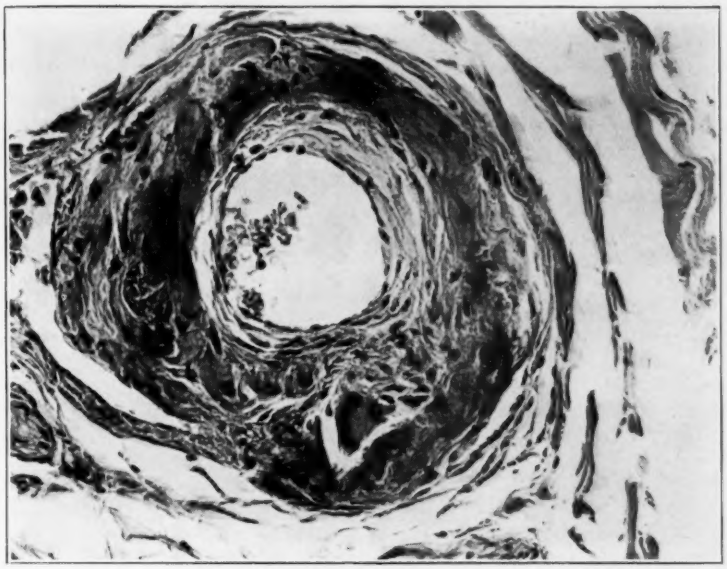

Fig. 1.—Small artery in the adventitia of the femoral nerve. The media has been replaced by amyloid, which is collected into small masses, some of which are surrounded by foreign body giant cells. Congo red stain; × 275.

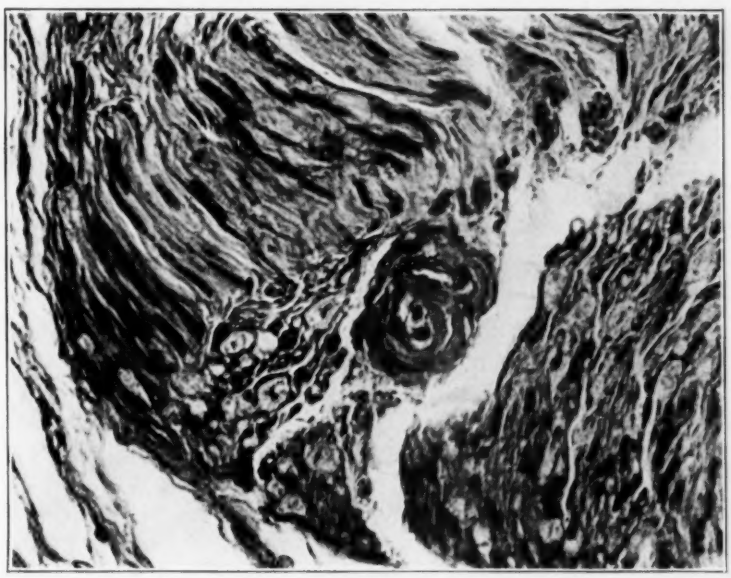

Fig. 2.—Arterioles in the right femoral nerve. Small masses of amyloid have replaced the media and have narrowed the lumen of the vessels. Some vessels were occluded. Congo red stain; × 450.

We regret that the central nervous system was not available for study, but we obtained the femoral and sciatic nerves and the brachial plexus for study, as well as portions of the sympathetic nervous system.

The most conspicuous changes in the various nerve bundles were in the arteries and arterioles between and within the bundles. The media of these vessels had been replaced by masses of amyloid (fig. 1). Some of these masses had encroached on the intima, producing partial occlusion of all and complete occlusion of some vessels. The larger vessels between the nerve bundles were damaged more severely than the smaller ones (fig. 1). The amyloid, as in other tissues, had

Fig. 3.—Extensive degeneration and disappearance of most of the myelin sheaths (right sciatic nerve). Weigert myelin sheath stain; × 200.

spread beyond the adventitia and into the perivascular connective tissue. Around many of the masses of amyloid there were large, multinucleated foreign body giant cells (fig. 1).

The only amyloid within the nerve bundles was that in the walls of the small arteries and arterioles (fig. 2). It had not spread into the connective tissue around or within the nerve bundles or around the individual myelin sheaths. In no place were the myelin sheaths compressed or crushed by the amyloid. With the myelin sheath stains we noted extensive degeneration of the nerve bundles (fig. 3). In some places small, and in others large, portions of

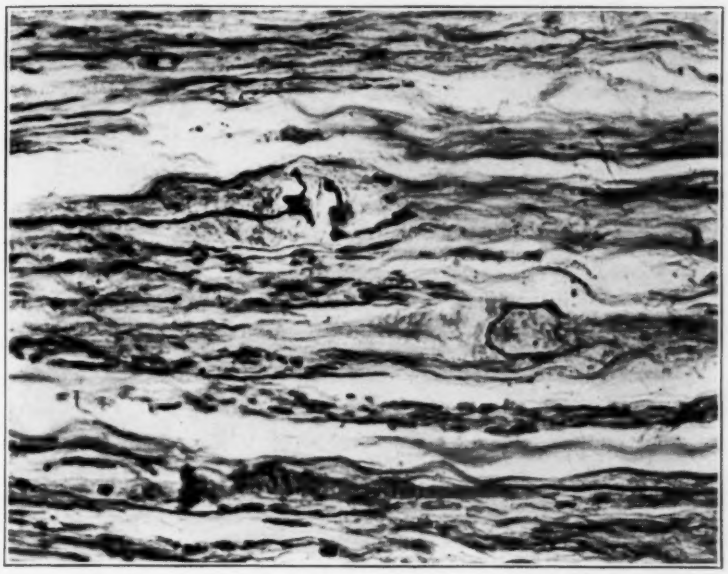

Fig. 4.—Degeneration, fragmentation, clumping and beading of some axis-cylinders (femoral nerve). Some have completely degenerated, and few are normal. Orlandi silver impregnation stain; × 450.

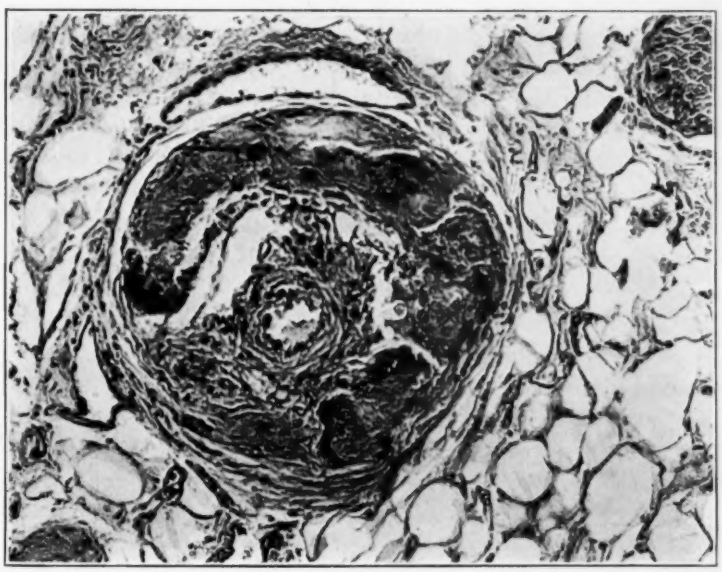

Fig. 5.—Small artery from the sympathetic nervous system, showing extensive amyloid degeneration of the media, which has been replaced and the masses surrounded by foreign body giant cells. Note the extreme narrowing of the lumen of the vessel. Hematoxylin and eosin stain; × 165.

the nerve bundles were degenerated, so much so that entire bundles had been destroyed and replaced by connective tissue or sheath of Schwann cells, and these portions did not contain amyloid. Orlandi and Bodian silver impregnation methods showed many portions devoid of axis-cylinders, while in some places active degeneration was taking place (fig. 4). We did not observe any evidence of regeneration of the degenerated axis-cylinders. With fat stains we observed degeneration of myelin sheaths. In some nerve bundles there were small collections of lymphocytes around some of the blood vessels. Undoubtedly, these lymphocytes were partially the result of tissue degeneration and partially the reaction to the foreign material, amyloid. The blood vessels in the sympathetic nervous system showed similar changes (fig. 5).

COMMENT

For many years amyloidosis was thought to be secondary to prolonged sepsis; however, more recent experiences have indicated that widespread amyloid changes may occur independently of sepsis. The amyloidosis in the case presented in the preceding paragraphs belonged to this nonseptic type, since there was no history of sepsis and no evidence of sepsis was observed at necropsy.

In some of the cases of nonseptic amyloidosis which we have studied, the disease process was limited fairly sharply to the media of the smaller arteries and arterioles. In the case presented in the preceding paragraphs the masses of amyloid had spread in most organs beyond the media of the blood vessels, through the adventitia and into the surrounding connective tissue. The connective tissue had not undergone any amyloid change but did react by surrounding the small masses of amyloid with foreign body giant cells. The amyloidosis of the small arteries and arterioles had produced narrowing of the lumen of the vessels and in many places had occluded them completely. The changes in the parenchyma of the various organs were the result of ischemia subsequent to the narrowing or occlusion of the blood vessels by the amyloid, and not of amyloid changes in the parenchyma of the organs. The results of the ischemia were seen best in the peripheral nerves, where there was extensive degeneration. The degeneration in the peripheral nerves should be considered the result of the ischemia and properly should be termed ischemic neuritis or ischemic neuropathy. The weakness of which the patient complained must be attributed to the changes in the nerves and not to amyloid changes in the skeletal muscles, which were involved only slightly by the amyloidosis. We had available for study peripheral nerves from 13 other cases of generalized amyloidosis, and in none of these was there any degeneration comparable to that seen in the present case.

The central and peripheral nervous systems are considered to be remarkably immune to amyloidosis—even to the secondary effects of amyloid changes—and, except for the 1 case described in this paper, our experience would conform to the generally accepted opinion.

SECTION OF THE CEPHALIC THIRD OF THE VAGUS–SPINAL ACCESSORY COMPLEX

CLINICAL AND HISTOLOGIC RESULTS

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It has been demonstrated [1] that the vagus–spinal accessory complex contains some roots which are chiefly sensory and others which are chiefly motor. The possibility of operative severance of that portion of the complex which is predominantly sensory in cases of intractable pain was thereby suggested. The present communication deals with a case in which approximately the cephalic third of the roots of the vagus–spinal accessory complex was divided in an attempt to abolish pain in the head and in which the opportunity for studying the brain stem later presented itself.

REPORT OF A CASE

A man aged 57 was admitted to the Beth Israel Hospital, Newark, N. J., under the care of Dr. William Ehrlich, with a diagnosis of carcinoma of the tongue which involved the glands of his neck. He complained of severe pain on the right side of his head "coming out of the ear." The pain was so intense, requiring opiates, that the patient was willing to undergo any procedure which offered the possibility of giving him some relief. In view of the fact that the component of the pain which radiated from his ear was very severe, and that the vagus nerve is known to contribute to the tympanic plexus through Arnold's nerve, it was considered justifiable to attempt division of the cephalic portion of the vagus–spinal accessory complex, which is chiefly sensory. Suboccipital craniotomy was performed, and the cephalic third of the right vagus–spinal accessory roots, exclusive of the spinal portion, was divided (fig. 1). A transient rise in pulse rate and blood pressure followed the operation (fig. 2). On the first postoperative day the systolic blood pressure was maintained at a somewhat higher level than before operation, but unfortunately no blood pressure readings were subsequently recorded. No change in speech or difficulty in swallowing followed operation. Examination,

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Read before the American Association of Neuropathologists, Atlantic City, N. J., June 9, 1941.

From the Neurosurgical Service and the Division of Laboratories of the Jewish Hospital of Brooklyn and the Division of Laboratories of the Beth Israel Hospital of Newark, N. J.

1. Tarlov, I. M.: Structure of the Nerve Root: II. Differentiation of Sensory from Motor Roots; Observations on Identification of Function in Roots of Mixed Cranial Nerves, Arch. Neurol. & Psychiat. **37**:1338 (June) 1937; The Sensory and the Motor Roots of the Glossopharyngeal Nerve and the Vagus-Spinal Accessory Complex, ibid. **44**:1018 (Nov.) 1940.

Fig. 1.—Photograph of the brain stem, showing tip of silver clip (*S*) on the cephalic vagus roots, which were cut at operation.

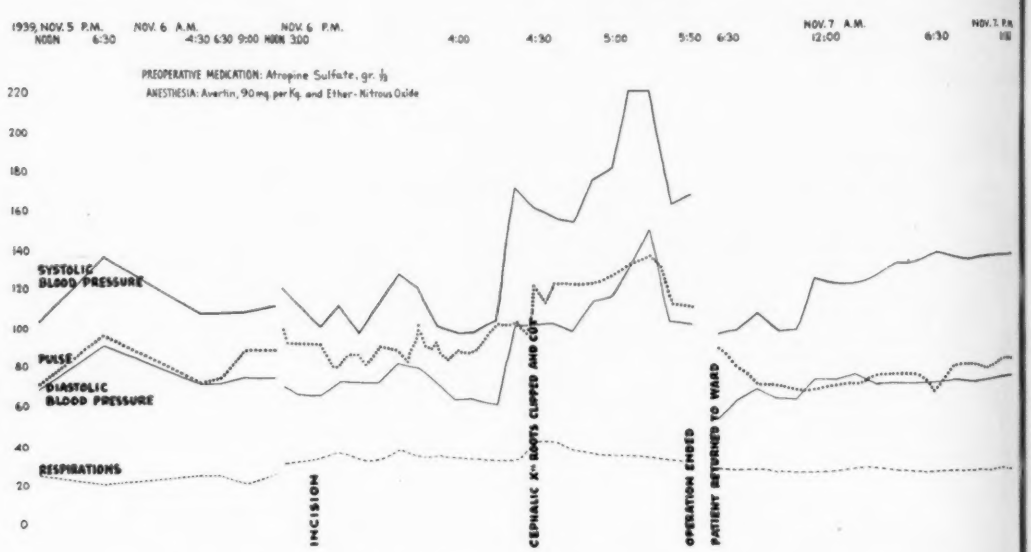

Fig. 2.—Chart showing blood pressure and pulse and respiratory rates before and after operation in the case of a man aged 57.

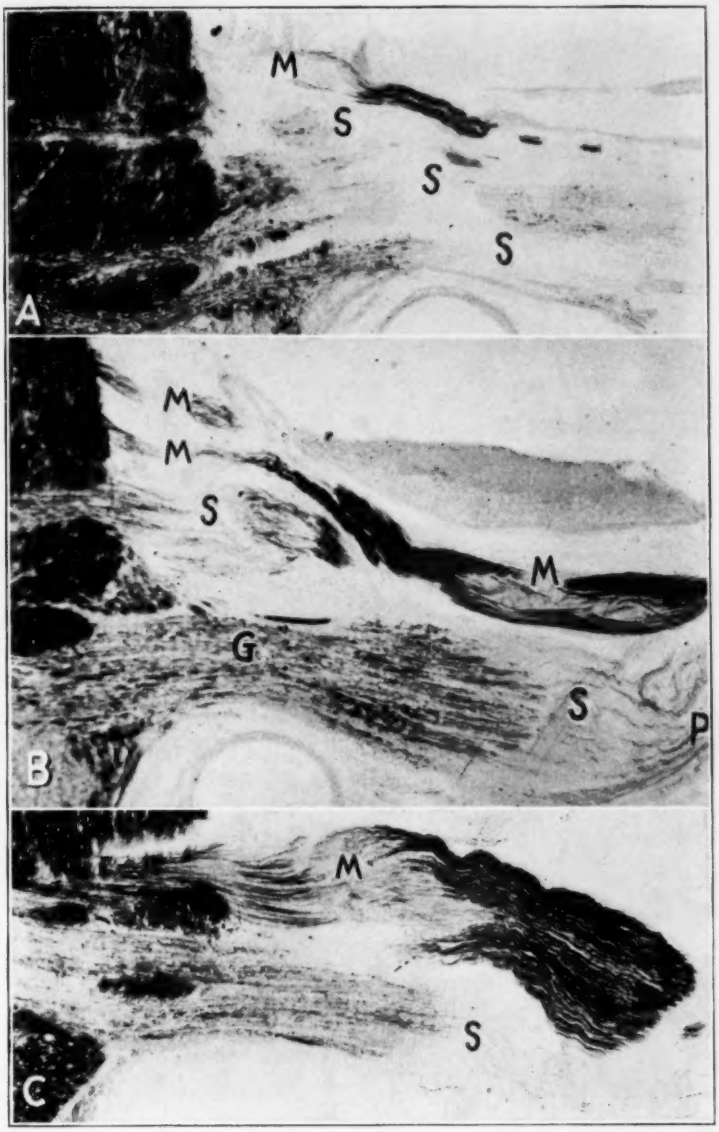

Fig. 3.—Photomicrographs are arranged consecutively from the most cephalic (*A*) to the most caudal (*C*) sections through the vagus roots, which were divided at operation. Weigert-Pal technic; × 40.

Note (1) the marked fragmentation and rarefaction of myelin in the dorsal sensory roots (*S*), in contrast to the intact myelin sheaths of the ventral roots (*M*), (2) the gradual decrease in size of the sensory and the increase in size of the motor roots in a caudal direction and (3) the decrease in number of intact myelin sheaths in *B* as one passes from the peripheral nonglial segment (*P*) to the central glial segment (*G*) of the nerve root.

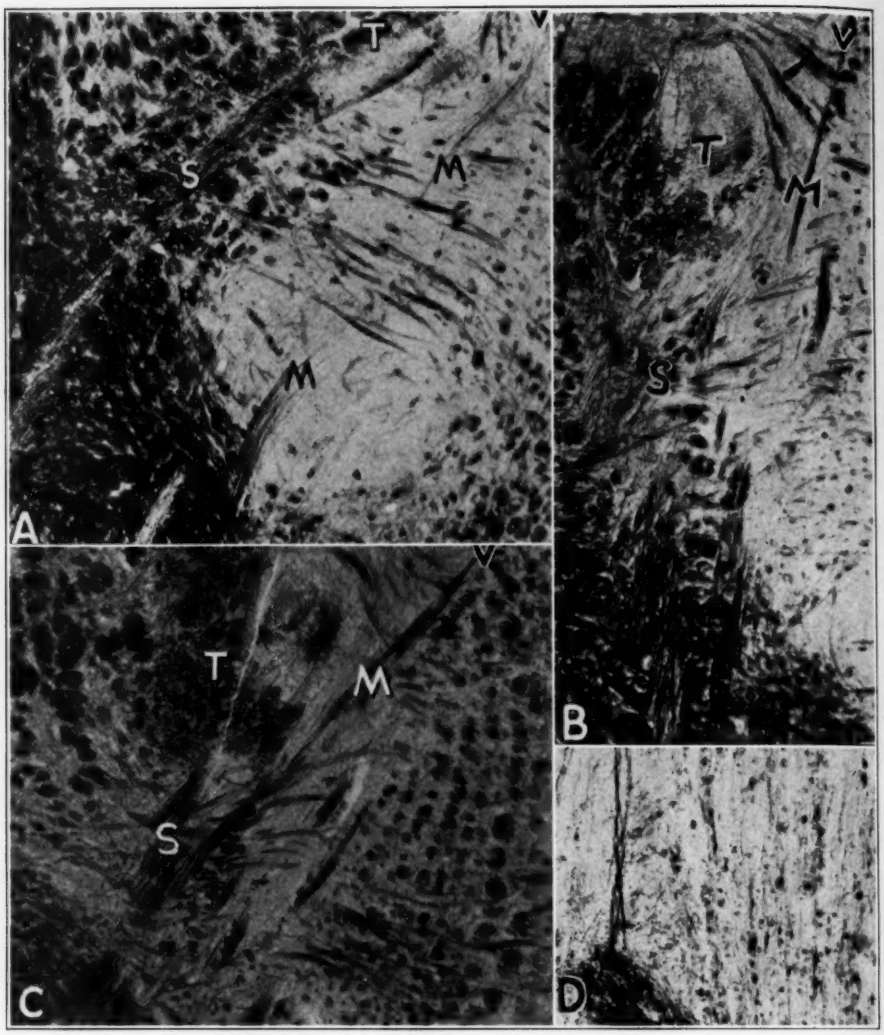

Fig. 4.—Photomicrographs. *A*, cephalic part of divided vagus roots, showing fragmented and rarefied myelin sheaths representing fibers of the dorsal sensory root (*S*) entering the nucleus of the tractus solitarius (*T*). The myelinated fibers of the small ventral root (*M*) shown in figure 3, arising from the region of the dorsal motor nucleus of the vagus nerve (*V*), are intact. Weigert-Pal technic; × 40.

B, caudal part of divided vagus roots, showing intact myelinated nerve fibers (*M*) diverging from a bundle of myelinated nerve fibers (*S*), most of which are degenerated, to establish connection in the region of the dorsal motor nucleus of the vagus nerve (*V*). Weigert-Pal technic; × 40.

C, section just caudal to the divided vagus roots, showing bundle of sensory myelinated nerve fibers (*S*) entering the nucleus of the tractus solitarius (*T*) and motor myelinated nerve fibers (*M*) arising from the region of the dorsal motor nucleus of the vagus (*V*). Weigert-Pal technic; × 40.

D, an occasional intact myelin sheath in the glial portion of the dorsal sensory root of the divided vagus roots. Weigert-Pal technic; × 120.

including laryngoscopic studies, failed to reveal paralysis of the palate, pharynx or vocal cords. Sensation over the soft palate and posterior pharyngeal wall was normal. Laryngoscopic examination ten days after operation (Dr. Nathan Zvaifler and Dr. William Ehrlich) indicated absence of pain over the right side of the epiglottis. It was the examiners' impression that the right lower portion of the pharynx, as well as the larynx, showed diminished sensitivity to pain. Tests of salivary secretion from the parotid and the submaxillary and sublingual glands revealed no appreciable differences in the weighed amount of secretion before and after operation. Taste sensation was unaltered. Electrocardiograms and gastric analyses before and after operation revealed no significant change. The pain on the right side of his head continued, but it no longer radiated from his ear. While further sectioning of nerve roots was being planned in an attempt to relieve the pain, the patient suddenly died, forty-five days after operation, as a result of hemorrhage from a large vessel of the neck which was invaded by the primary tumor.

Anatomic Study.—Serial sections of the brain stem from the cephalic end of the glossopharyngeal roots to the caudal region of the vagus–spinal accessory roots were cut and stained for myelin by the Weigert-Pal technic.

Preparations through the glossopharyngeal nerve roots showed a thick bundle of well medullated nerve fibers which entered the nucleus of the tractus solitarius and a small ventromedial bundle which arose from the region of the dorsal motor nucleus of the vagus nerve and, probably, also from the nucleus ambiguus. The myelin sheaths of all of these fibers were intact and showed no evidence of degeneration. In contrast to this, there was complete change of appearance in the cephalic vagus roots. The main dorsal cephalic trunk of the vagus nerve showed marked fragmentation and rarefaction of myelin (fig. 3). These degenerated nerve fibers entered the nucleus of the tractus solitarius (fig. 4 *A* and *B*). A small bundle of intact myelinated fibers arose from the region of the dorsal motor nucleus of the vagus nerve (fig. 4 *A* and *B*) and the nucleus ambiguus, forming the small ventromedial root of the vagus (fig. 3). Fragmentation of a myelin sheath was rarely encountered in this root. In some of the sections an intermediate root between the main dorsal degenerated root and the small ventromedial nondegenerated root appeared. About three fourths of the myelin sheaths of this intermediate root showed marked fragmentation. Only an occasional intact myelin sheath was present in the main dorsal root of the vagus nerve, which showed the marked degenerative change. These intact myelinated fibers of the main dorsal root (fig. 4 *D*) represented approximately 5 per cent of the total number of fibers and, like those of the intermediate root, were of a smaller average caliber than those of the small ventromedial root, which arose directly from the dorsal motor nucleus of the vagus and the nucleus ambiguus. The intact myelinated fibers of the main dorsal root of the vagus nerve joined those of the intermediate root and diverged from the main bundles of degenerated myelinated fibers to establish connection in the region of the dorsal motor nucleus of the vagus (fig. 4 *B*). The degenerated main bundle entered the nucleus of the tractus solitarius.

Passing caudally along the vagus roots, one observed an increase in number of intact myelinated fibers which arose from the region of the motor nuclei of the vagus nerve (fig. 3) and a decrease in the fibers with fragmented myelin sheaths which terminated in the nucleus of the tractus solitarius. The last sections through the divided cephalic roots contained more than one half of the intact myelinated fibers which arose from the dorsal motor nucleus of the vagus and the nucleus ambiguus.

As one proceeded caudally from the divided roots, an increasing predominance of myelinated fibers arising from the dorsal motor nucleus of the vagus and the nucleus ambiguus was observed (fig. 4 *C*). Approximately one third of the myelinated fibers at this level formed the dorsolateral bundle which entered the nucleus of the tractus solitarius. These steadily decreased in numbers in successive sections, finally disappearing about 1 mm. caudal to the most caudad portion of the divided roots.

The tractus solitarius at the level of the divided roots appeared somewhat rarefied. This rarefaction became inconspicuous caudal to the divided roots.

The intact myelin sheaths in the large dorsal root and the intermediate root of the vagus nerve decreased as one passed from the peripheral nonglial to the central glial segment of the roots proximal to the site of operative division. Preparations of the cephalic vagus roots distal to the point of severance showed a marked decrease in the number of myelin sheaths as compared with preparations taken from the opposite, intact side. Whether these intact myelin sheaths of the cephalic vagus roots on the side of operation represented sensory or motor fibers could not be determined. Cresyl violet stains of the ganglia of the vagus nerve on this side showed intact as well as chromatolytic ganglion cells.

COMMENT

The clinical changes which followed division of the cephalic third of the vagus–spinal accessory complex were of a sensory nature. The rises in pulse rate and blood pressure were transient. Although some motor fibers were cut, as was proved histologically, these fibers apparently were unimportant for the maintenance of the pulse and respiratory rates and blood pressure and for normal palatal, pharyngeal or laryngeal movements. In another case in which the cephalic half of the vagus–spinal accessory complex was divided, paralysis of the homolateral side of the palate, pharynx and larynx, in addition to loss of sensation over the homolateral side of the larynx, was observed. It is of interest that in the latter case recovery from the palatal, pharyngeal and laryngeal paralysis was practically complete seven months after operation. Observations in these 2 cases indicate that the motor fibers innervating the palate, pharynx and larynx reside more caudal than the cephalic third, and largely within the cephalic half, of the vagus–spinal accessory roots. In the case in which the cephalic half of the vagus–spinal accessory roots was cut, sensory examination for the first five days after operation revealed homolateral absence of appreciation of painful and tactile stimuli over the soft palate and pharynx as well as the larynx. There was gradual return of sensation over the soft palate and pharynx, sensation becoming normal on the fifteenth postoperative day. Absence of sensation over the larynx persisted. It seems likely that the early transient sensory impairment over the area (soft palate and pharynx) which is supplied with sensory fibers from the glossopharyngeal nerve might be due to either one of two possible causes: (1) slight recoverable trauma to the glossopharyngeal roots during section of the contiguous

vagus roots, or (2) temporary interruption of conduction within the nucleus of the tractus solitarius resulting from mild inflammatory changes secondary to degeneration of the afferent vagus fibers. The nucleus of the tractus solitarius is the nucleus of reception for afferent fibers from the glossopharyngeal and the vagus roots. On the basis of either of the aforementioned mechanisms, division of the sensory roots of one nerve may, for a short time, block physiologic conduction from the other nerve. Either of these mechanisms might also explain the diminution in sensation over the lower part of the pharynx in the case in which the cephalic third of the vagus–spinal accessory complex was cut. It is possible that laryngoscopic examination, if performed after the twelfth day, might have disclosed recession of the zone of sensory impairment from the pharynx. Numerous studies following intracranial section of the glossopharyngeal nerve have made it clear that this nerve supplies sensation to the soft palate, uvula and pharynx.[2] The experiences herein recorded indicate that the larynx is supplied with sensation by the vagus nerve.

All of the sensory fibers of the cut vagus roots entered the region of the nucleus of the tractus solitarius. That not all of the sensory fibers are contained within the cephalic third of the vagus–spinal accessory complex was indicated by the fact that caudal to the divided roots some intact fibers were seen which entered the nucleus of the tractus solitarius. These sensory fibers disappeared within the next caudal millimeter of the roots.

The differences in degeneration in sensory and motor nerve roots were clearly demonstrated in these sections. Motor roots which arose from the dorsal motor nucleus of the vagus nerve and the nucleus ambiguus showed intact myelin sheaths up to the point of nerve root section. The large dorsal sensory root showed fragmentation of myelin sheaths up to the nucleus of the tractus solitarius. The few fibers with intact myelin sheaths within this large root diverged from the main sensory tract just proximal to the nucleus of the tractus solitarius to enter the region of the dorsal motor nucleus of the vagus nerve. It is apparent, therefore, that this large dorsal cephalic root, while predominantly sensory, contained a few motor fibers. The occurrence of these intact myelinated fibers from the dorsal motor nucleus of the vagus nerve in greater numbers in the intermediate root, which made its appearance in some sections, indicated that there was a gradual transition from the large dorsal, predominantly sensory root, to the small ventromedial, motor root. A similar transition from the pre-

2. Erickson, T. C.: Paroxysmal Neuralgia of the Tympanic Branch of the Glossopharyngeal Nerve: Report of Case in Which Relief Was Obtained by Intracranial Section of Glossopharyngeal Nerve, Arch. Neurol. & Psychiat. **35**: 1070 (May) 1936.

dominantly sensory cephalic roots to the predominantly motor caudal roots occurred. The fact that there was but a rare fragmented myelinated fiber which arose from the dorsal nucleus of the vagus nerve renders it unlikely that this nucleus contains any appreciable number of sensory cells.

There was a decrease in the number of myelinated fibers at the transition point from the peripheral nonglial to the central glial segment of the large dorsal nerve root. More myelinated fibers were present on the peripheral side of the transition zone, proximal to the site of operative section.[3] This observation would indicate that some attempt at regeneration of these sensory fibers did occur, the attempt being thwarted at the transition zone. The absence of Schwann cells in the central glial segment of the nerve root probably accounts for the inability of sensory fibers to regenerate completely. From this material it could not be determined whether the motor fibers regenerated beyond the point of operative section. Preliminary unpublished experiments on animals indicate that motor roots may regenerate. Also, the observations in the second case, in which palatal, pharyngeal and laryngeal paralysis almost entirely cleared up seven months after operation, indicate that regeneration of motor roots may occur.

CONCLUSIONS

Operative section of the cephalic third of the vagus–spinal accessory complex was followed by sensory changes over the larynx and lower portion of the pharynx; no evidence of disturbance of motor function, other than transient rise in pulse rate and blood pressure, occurred.

After section of the cephalic third of the vagus–spinal accessory complex, motor fibers central to the section remained intact while sensory fibers showed evidence of degeneration up to the nucleus of the tractus solitarius. It was thus possible to differentiate clearly sensory from motor fibers in the cut roots.

Most of the sensory fibers of the vagus nerve are contained within the cephalic third, approximately, of the vagus–spinal accessory complex. These sensory fibers occur within the large dorsal roots, which also contain a few motor fibers.

3. The exact relation of fibers central and distal to the site of operative section could not be determined. Nor could accurate counts of the relative numbers of nerve fibers or of ganglion cells on the two sides be made, since the entire vagus nerves and their ganglia were not available for study.

News and Comment

PSYCHIATRIC INTERNSHIPS IN BELLEVUE HOSPITAL

The Psychiatric Division of Bellevue Hospital announces a new type of two year internship beginning July 1, 1942. Twelve two year internships will be open to graduates of class A medical schools, and previous hospital experience is not necessary. It is expected that these internships will give the required year of medicine and surgery so that those who are going on in psychiatry will not have to take a general hospital internship. The first year will consist of six months in medicine and six months in surgery in the medical and surgical wards of the Psychiatric Division. The interns in the medical and the surgical service will be responsible for the psychiatric as well as the medical and surgical work-up of their cases. In the medical service the psychosomatic relationship will be stressed, and the service will be known as a service in psychosomatic medicine. In other words, the intern will be expected to study the total personality and to work up the case from all angles, including the psychiatric. In the surgical service the same idea will be stressed, particularly in relation to the head injuries, on which an excellent amount of material will be available for more complete and adequate study.

During the second year the intern will work in the various psychiatric wards but will continue to utilize his medical and surgical training and will make all necessary physical examinations and will carry out medical and surgical procedures in his own ward.

In addition to these 12 two year internships, there will be 4 one year internships, which will correspond to the second year of the two year internship and which will be open to graduates of class A medical schools who have had one year of a general hospital internship.

Applications for such internships should be made to the office of the director (Carter N. Colbert, M.D., Acting Director) of the Psychiatric Division of Bellevue Hospital.

BRAIN DISEASE REGISTRY, WAYNE UNIVERSITY COLLEGE OF MEDICINE, DETROIT

Metropolitan Detroit, with a population of about 2,000,000 inhabitants, provided a unique opportunity for the establishment of a Brain Disease Registry. There are twelve larger hospitals and thirteen smaller ones, a total of twenty-five hospitals, which have well organized departments of pathology and pathologists interested in neuropathology, without having sufficient time or trained personnel for neuropathologic examination. Since there was no neuropathologic laboratory before, there was no adequate examination of organic diseases of the central nervous system. With the aid of the progressive dean of the Wayne University College of Medicine, Dr. Edgar H. Norris, it was possible to organize a Brain Disease Registry, which has been created under the auspices of the Department of Pathology and under the direction of Dr. Gabriel Steiner. In addition to the departments of pathology of the various hospitals, the facilities of the Brain Dis-

ease Registry are available to physicians and research workers. The services of the Brain Disease Registry include storage of tissue specimens for examination and research, reports to the various departments of pathology, statistics on the examined cases, teaching and demonstration facilities and publications.

BEQUESTS TO NEW YORK UNIVERSITY FROM DR. MENAS S. GREGORY

Dr. Menas S. Gregory, who died on Nov. 2, 1941, made two bequests, totaling $40,000, for the benefit of psychiatry in New York city.

The first was a trust fund of $20,000 given to New York University, the income of which is to be devoted to the purpose of establishing a Menas Gregory lectureship in psychiatry. The selection of the lecturers and the regulation of details of the lecture or lectures are to be made by a committee consisting of the professor of psychiatry of New York University, the president of the New York Neurological Society and the chairman of the Section on Neurology and Psychiatry of the New York Academy of Medicine.

"Such lectures should be published for distribution to the various medical libraries and not more than one-fifth of the income should be devoted to the publication and distribution of the lectures. In the event of any surplus in any one year the committee is at liberty to carry such surplus over to another year or to invest the same in psychiatric literature for Bellevue Psychiatric Hospital." The will provides that "the subject of such lecture or lectures shall be intensely practical and useful and be confined to the discussion and review of the latest discoveries in the treatment and care of the mentally sick during the current year." They are to be delivered by "the most outstanding and available psychiatrist, either of this country or from abroad," at the Bellevue Hospital or New York University.

The second bequest is a trust fund of $20,000 left to New York University, the income of which is to be devoted to endowing a Menas Gregory professorship in psychiatry at New York University.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

FIBRILLARY TWITCHINGS. C. H. SHELDEN and H. W. WOLTMAN, Am. J. M. Sc. **201**:831 (June) 1941.

Shelden and Woltman were interested in determining the origin of fibrillations in such diseases as progressive muscular atrophy, progressive bulbar paralysis and amyotrophic lateral sclerosis and in the question whether a peripheral mechanism accounted for the fibrillation. They performed an experiment on an elderly man who suffered from amyotrophic lateral sclerosis with generalized fibrillary twitching in both lower extremities. To effect spinal anesthesia, 70 mg. of procaine hydrochloride in 2 cc. of cerebrospinal fluid was administered. Complete motor and sensory paralysis was obtained well above the level of the umbilicus. Fibrillary twitchings in the exposed and other muscles continued unchanged. A few days later peripheral block of the left common peroneal nerve was accomplished, using metycaine. There was no visible change in the diffuse fibrillary twitchings of the involved peroneal muscles. The authors believe that these observations exclude the bodies of the cells of the anterior horn as the site of involvement, as fibrillation in the lower extremities persisted under the influence of spinal anesthesia or block of the nerve to an involved area. It is concluded that future studies of fibrillation should be addressed to the peripheral portions of the neuromuscular unit rather than to the cell body itself.

MICHAELS, Boston.

PHYSIOLOGICAL AND PHARMACOLOGICAL INVESTIGATION ON THE NATURE OF HYPOTHALAMIC EXCITATION. ERNST GELLHORN, Am. J. Psychiat. **97**:944 (Jan.) 1941.

Gellhorn, working with cats anesthetized with chloralosane (a compound of chloral hydrate and dextrose), stimulated the hypothalamus and produced contraction of the nictitating membrane of the same side. Stimulation of the cervical portion of the sympathetic trunk on the opposite side yielded the same result. With this preparation the effect of various drugs was studied, and Gellhorn concluded that anoxia, hypercardia, and convulsant drugs, especially metrazol, stimulated the hypothalamic sympathetic centers. By differential section and ablation of the vagus nerves and the adrenal glands, Gellhorn concluded that metrazol and anoxia simultaneously stimulate both the vagoinsulin and the sympatheticoadrenal system.

Gellhorn produced rage responses by stimulating the hypothalamus with a rise in the blood sugar. Stimulation of the hypothalamus combined with adrenalectomy and denervation of the liver led to hypoglycemia, but with section of the vagus nerves the hypoglycemic effect disappeared. He concluded that sham rage is characterized by a discharge over both systems. From these experiments, and from those on a spinal cat, Gellhorn concluded that emotion results in both vagal and sympathetic stimulation.

FORSTER, Boston.

SYNDROME OF THE DESTRUCTION OF THE PINEAL GLAND. JOHN MARTIN and LOYAL DAVIS, Arch. Int. Med. **67**:1119 (June) 1941.

Martin and Davis made an experimental investigation of the extirpation of the pineal gland in rats, cats, dogs and monkeys, with a follow-up study of these animals over a period of four and one-half years. The pineal gland was destroyed

with the aid of the Horsley-Clarke stereotaxic instrument, and animals from the same litters, not pinealectomized, were used as controls. Cats were used extensively because they are well adapted to this purpose.

There were no significant differences in the somatic development of the control and the pinealectomized female cats. It was noted that the normal cats experienced estrus at an earlier date than did those which had been operated on. Pinealectomized mother cats had small litters which they tended to drop three or four days before term, with the kittens dead or very feeble. The pinealectomized mothers showed little maternal instinct.

The average normal male cat shows no sexual interest before 13 or 14 months of age, but at approximately 9 months of age the pinealectomized males showed definite sexual interest. They had longer genitalia, were heavier and had bigger skeletons than had their control mates.

The files of the Cushing tumor registry were reviewed, and 18 cases classified under "Tumors of the Pineal Gland" were found. All these cases were verified either at autopsy or at operation. When these patients' symptoms and signs were compared with the changes observed in the laboratory animals, certain significant differences were noted. None of the animals showed polydipsia, emaciation, polyuria, obesity, somnolence, hypothalamic stupidity or infantilism. Both male patients and animals showed early somatic and sexual development, with a corresponding maturity in behavior.

In keeping with the less prominent somatic changes in the female patients, the female pinealectomized animals showed no premature body growth. The amenorrhea which occurs in the female patients may be compared with the delay in the first estrus in the pinealectomized female animals and their subsequent variations from the normal reproductive activity.

It seems certain that the simple primary destruction of the pineal gland in the laboratory animal differs markedly from the manifestations which occur in man as a result of tumor invasion. The latter is usually attended by associated pathologic changes extending beyond the pineal gland itself, into the vegetative centers of the diencephalon.

BECK, Buffalo.

EFFECT OF LOW AND HIGH OXYGEN TENSIONS ON MENTAL FUNCTIONING. A. L. BARACH, J. Aviation Med. **12**:30 (March) 1941.

Barach compared the effects of low and high oxygen concentrations on the mental activity of 17 medical students and 9 psychoneurotic patients. The subjects breathed an atmosphere of 13 per cent oxygen (equivalent to an altitude of 12,400 feet [3.7 kilometers]) for three hours. Impairment of emotional control was demonstrated in all 17 students. In 50 per cent elation and overconfidence were first manifested; these conditions were followed by headache and lethargy. In 41 per cent mental dulness continued throughout the experiment, with headache at its termination. The patients showed more pronounced lack of emotional restraint, exaggerated self esteem and inability to inhibit instinctive drives. The mood of 5 patients changed from a hypomanic state to dulness and lethargy, and 4 patients had dulness and apathy from the beginning. A phenomenon not generally recognized is that inhalation of 50 per cent oxygen in patients with previously existing chronic anoxia may temporarily produce a profound disturbance in mental functioning. This is likely to occur especially in cases of pulmonary emphysema and pulmonary fibrosis in which the arterial oxygen saturation has been lowered over a long period. Deep sleep and stupor occurred, followed in some instances by coma and delirium. Milder manifestations were headache, depression and a variable degree of irrationality. When the patients became acclimatized to the increased oxygen tension the mental disturbance disappeared and was followed by a cheerful and optimistic mood. In most instances the duration of the disorder produced by inhaling 50 per cent oxygen lasted for from two to four days; in 1 a deep sleep verging on coma lasted for seven days. Inhalation of high oxygen atmospheres did not alter the mental function of normal subjects.

J. A. M. A.

STUDIES ON THE PHOSPHORUS COMPOUNDS OF BRAIN: II. ADENOSINE TRIPHOSPHATE. STANLEY E. KERR, J. Biol. Chem. **140**:77, 1941.

Adenosine triphosphoric acid was isolated as the dibarium salt from dog brain, with a yield of 70 per cent. By alkaline hydrolysis of the triphosphate crystalline adenylic acid was prepared, with a melting point identical with that of myoadenylic acid. A mixture of the two showed no depression of the melting point.

PAGE, Indianapolis.

THE EFFECT OF CHOLIN-LIKE SUBSTANCES ON THE CEREBRAL ELECTRICAL DISCHARGES IN EPILEPSY. D. WILLIAMS, J. Neurol. & Psychiat. **4**:32 (Jan.) 1941.

Williams investigated the effect of acetylcholine and allied drugs on the incidence of epileptic cerebral discharges in cases of petit mal epilepsy. The discharges referred to those seen in the electroencephalographic records of clinical and subclinical attacks, both those occurring spontaneously and those induced by overbreathing. The author was able to corroborate observations in previous investigations that small subcutaneous injections of physostigmine salicylate (1.0 mg.) decreased and larger doses increased petit mal activity, while prostigmine invariably caused an increase in the number of attacks. Carbaminoylcholine chloride injected subcutaneously in doses of 0.25 mg. caused an increase in both the incidence and the duration of the attacks, whether spontaneous or induced, while in predisposed subjects discharges were precipitated. There were no untoward clinical effects. Previous subcutaneous injection of atropine sulfate (grain, $\frac{1}{100}$ [0.6 mg.]) abolished or diminished the effect of carbaminoylcholine chloride. In 2 patients with petit mal and psychomotor epilepsy intravenous injection of 30 to 60 mg. of acetylcholine produced attacks, the attacks being similar to those usually experienced by the patient. The characteristic clinical reactions of acetylcholine, in the form of initial bradycardia followed by tachycardia, coughing, flushing of the face, sweating, a sensation of constriction in the chest and throat and slight substernal pain, were observed. There was no increase in epileptic activity when the drug was injected along with intravenous administration of $\frac{1}{150}$ grain (0.4 mg.) of atropine sulfate. Subcutaneous injections of atropine sulfate in doses of $\frac{1}{150}$ to $\frac{1}{100}$ grain (0.4 to 0.6 mg.) as a rule failed to reduce the number of attacks. There was no epileptic discharge in normal control subjects. Histamine, pilocarpine and apomorphine produced no change in the incidence of the epileptic cerebral discharges, so that other factors could be excluded in the action of the choline-like substances. The similar action of these drugs in increasing epileptic activity and the inhibition of such discharges by atropine suggest that the changes are related to an alteration in the acetylcholine-transmitting mechanism somewhere in the body. The effect may be an indirect one, due to peripheral changes, or it may be direct and due to alerations in the central nervous system. Although the causative factors are not definitely known, the author feels that the coincidental changes in respiratory exchange, the p_H of the blood, the blood sugar level and the cerebral blood flow are not responsible for the changes in epileptic activity.

MALAMUD, Ann Arbor, Mich.

CENTRAL REGULATION OF THE WHITE BLOOD CELLS. RAINER HOPPE, Ztschr. f. d. ges. Neurol. u. Psychiat. **169**:700 (June) 1940.

White blood counts were made in 65 cases before and after pneumoencephalography and in 20 cases before and after various operations on the skull. In 55 of the 65 cases in which the ventricles were filled with air an increase in the white cell count of 1,000 or more was noted (85 per cent). In most of these cases there was an increase in the neutrophils, and in 21, a shift to the left. There seemed to be no difference in the increase in white cells between the cases in which the third ventricle was filled and those in which this ventricle was not visualized. It seems, therefore, that the cause of the increase in white cells cannot be attributed to

irritation of a hypothetic center in the floor of the third ventricle. Leukocytosis was found in every one of 20 cases immediately after an intracranial operation. It is evident that this postoperative leukocytosis cannot be considered in any way as caused by a disturbance in the hypothalamic region. The loss of blood and the operative procedure itself can account for the increased white cell count. There is insufficient evidence for the existence of a center in the floor of the third ventricle which regulates the white cells in the blood. SAVITSKY, New York.

THE NATURE OF PAIN IN HIGH FLIGHTS. V. V. STRELTSOV, Klin. med. (no. 9) **18**:42, 1940.

Streltsov calls attention to joint and muscle pain which develops when one is flying more than 10 kilometers above the sea level. The pathogenesis of this pain has not been elucidated. Haldane in 1909 suggested the possibility of caisson disease developing in rapid ascent to high levels. Benzinger called attention, in this connection, to the appearance of nitrogen bubbles in the cerebrospinal fluid as suggestive of increased intracranial pressure. The nerve tissue is first to undergo nitrogen desaturation because it consists chiefly of lipoids and nitrogen is more easily soluble in fats under the condition of lowered barometric pressure. Pain may be due to escape of nitrogen from nerve trunks or brain tissue. The pain may be of traumatic origin, since nitrogen bubbles are capable of tearing tissue or of exerting pressure on nerve trunks. Haldane made the observation that the brains of animals subjected to rapid decompression appear to be pierced by numerous bubbles, giving a vacuolated appearance. The author studied joint pain under the conditions of the low pressure chamber. Of 800 men subjected to barometric pressure of 197 mm. and less, which corresponds to height levels of from 10 to 14.5 kilometers, 55 (about 7 per cent) complained of joint pains. In personal experiments the author had noted that pain was first experienced in the small joints of the extremities and later in the large joints (shoulder, elbow, knee). A characteristic feature of the pain is its disappearance when the barometric pressure is increased. The pain as a rule disappears with the descent to levels below 10 kilometers. The author was not able to establish any relation between the development of the joint pain and the amount of oxygen inhaled. He stresses the importance of differentiating changes resulting from anoxemia from those due directly to lowered barometric pressure. He found that rabbits taken up in flights to 10 and 11 kilometers without oxygen supply died and exhibited postmortem pulmonary emphysema, hyperemia and hemorrhages into the lungs and intestinal mucosa and gas emboli in the large vessels and in the coronary vessels of the heart. Another factor of importance noted in cases of lowered barometric pressure is the loss of body temperature. The appearance of gas emboli and bubbles in the brain tissue is explained by loss of nitrogen, which, according to the Dalton-Henry law, passes, in a condition of lowered partial pressure, from a soluble to a gaseous state. Oxygen inhalation was suggested as a prophylactic measure before going on a flight. Theoretically, this should have the effect of lowering the partial pressure of nitrogen in the lungs, which in turn should lower its tension in the blood. This measure was effective in preventing caisson disease in divers. Prophylactic inhalation of oxygen for twenty minutes to three hours, followed by a rapid rise to from 10 to 14 kilometers, failed to have any effect on the development of the joint pain. The author likewise suggests that the origin of the pain may be sought in moderate or imperceptible anoxemia, such as takes place at moderate heights without oxygen inhalation or at great heights with oxygen inhalation. He thinks that this mild anoxemia is capable of disturbing the functional relation between the cortex of the brain and the subcortical tissue, with resulting imbalance between the stimulating and the inhibitory impulses. Such an imbalance may lead to increased sensitivity of the painful influences arising in the joints. The author regards the onset of joint pain as a danger signal signifying the approaching failure of compensatory physiologic mechanisms and requiring immediate descent to levels of higher atmospheric pressure. J. A. M. A.

Psychiatry and Psychopathology

THE INTERNAL ENVIRONMENT AND BEHAVIOR: V. INTERNAL SECRETIONS. CURT P. RICHTER, Am. J. Psychiat. **97**:878 (Jan.) 1941.

Richter demonstrated various attempts of animals to maintain constant their internal environment after different endocrine extirpations. These experiments included: 1. Removal of the posterior part of the pituitary gland, with resultant increase in fluid intake to maintain life and water balance. 2. Ablations of the thyroid or pituitary, with resultant decrease in temperature and attempts to offset this by building larger nests. 3. Adrenalectomy, followed by preference of saline solution rather than water, with sufficient intake of salt to maintain life. The animals, moreover, preferred sodium salts, particularly sodium chloride. 4. Removal of the parathyroid glands, followed by adequate and selective intake of calcium salts. Moreover, Richter and his associates found that, given a number of purified foodstuffs, the rats would of their own accord select a well balanced diet. That the preference of these animals for the particular foodstuffs which they require, such as sodium chloride after adrenalectomy, represents a chemotropic response rather than an attempt to obtain relief from discomfort was shown by the results of section of the gustatory nerves. After this operation the animals no longer chose the necessary foodstuff.

Richter concluded from these observations that the effort to maintain a constant internal environment constitutes one of the basic drives of human and animal behavior.

FORSTER, Boston.

RORSCHACH STUDIES IN ACUTE EXPERIMENTAL ALCOHOLIC INTOXICATION. DOUGLAS MCG. KELLEY and S. EUGENE BARRERA, Am. J. Psychiat. **97**:1341 (May) 1941.

Kelley and Barrera, wishing to validate the Rorschach method by experimental means, studied 10 subjects before and during mild acute alcoholic intoxication. The degree of intoxication was carefully controlled. Certain of the previous theoretic findings were validated. No pathognomonic Rorschach features of mild acute alcoholism could be determined. However, the authors found that the personality shifts occurring in this state of alcoholism could be correlated with shifts in the Rorschach response.

FORSTER, Boston.

PSYCHOSIS DURING ADMINISTRATION OF SULFANILAMIDE. J. R. WAUGH, Am. J. Syph., Gonor. & Ven. Dis. **25**:504 (July) 1941.

A 24 year old Negro with lymphogranuloma venereum and a chronic gonococcic infection of the prostate was given 2,430 grains (145.8 Gm.) of sulfanilamide from Jan. 25 to Feb. 23, 1940 and 600 grains (36 Gm.) from Feb. 23 to March 6, 1940. He became confused and disoriented; his attention was poorly maintained, and ideation was jumbled, with some flight of ideas. Seven days after the drug was discontinued, the sensorium became normal. Intensive oral administration of sulfanilamide was used in the treatment of 1,362 patients hospitalized in the genitourinary service. These patients usually received 960 grains (57.6 Gm.) of sulfanilamide, and in only one did psychotic behavior develop. Three others were confused and apathetic but recovered forty-eight hours after the drug was discontinued.

Several other instances of mental reactions are cited from the literature. In only one of these cases was there a fatal result, and in the others the disturbed behavior returned to normal soon after the drug was discontinued.

BECK, Buffalo.

THE REPETITIVE CORE OF NEUROSIS. LAWRENCE S. KUBIE, Psychoanalyt. Quart. **10**:23, 1941.

Kubie believes that the tendency to repeat is the nuclear problem in the neurosis. Repetition is the essence of all instinctual activity. In the child all

acquirement of skills takes place by a learning process that is based on repetition. The baby makes random attempts to relieve instinctual tensions. Some of these attempts are successful, so that the baby learns to repeat them. This brings skills. The child then uses this skill to obtain secondary gratifications, e. g., delight and triumph in mastery, to make a wordless appeal for love, praise or help and to express unformulated yearnings and wishes. In this way, one act in an infant may come to express the whole range of human feelings. Since all psychic phenomena are repetitive, neurotic manifestations are simply a distortion of this normal mechanism in that they represent repetition of specially selected situations. Obsessional neuroses and perversions are only special instances of this mechanism. In the obsessional neurosis there is conscious awareness of the mechanism of repetition, while in hysteria the awareness is unconscious. The single act of an infant by which it may express the whole range of human feelings becomes neurotic if the child cannot stop the act, cannot be distracted from it by substitute gratifications or be dissuaded by rewards or punishment; that is, it becomes neurotic if there is a change in flexibility. Why does this primary neurotic shift in flexibility occur? It does not seem to be the result of organic forces but occurs under psychologic influences, which may be analyzed as follows: 1. The satisfaction of an instinctual demand is delayed or frustrated. If the latter occurs, the child will attempt to restate his demands and, if unsuccessful, will suffer either a diffuse inhibition of activity leading to sleep or a temper tantrum. If the latter has to be stopped because it interferes with the child's relation to an adult, either a sense of guilt or a fear of retaliation develops; this inhibits the demand for satisfaction of instinctual needs. The unsatisfied need causes the child to experience a state of inner conflict which cannot be discharged adequately. Thereafter all that can occur are repetitions of substitute ways of getting satisfaction, which partly discharge tension and which meet with only mild adult displeasure. The act therefore becomes repetitive because it is a safe and permissible expression of (1) the original yearning; (2) anger at the original frustration; (3) feelings of guilt for the yearning and the rage, and (4) fear of retaliation for the anger and of the child's own deep resentments.

Since the act is the only possible expression of all these feelings and draws energy from all these sources, it becomes irresistible to the child and uncontrollable by the parents.

It is well known that all neurotic activity is the expression of paired antagonistic impulses; so it really is the civilized repression of a tantrum.

Kubie believes that the rigid repetition of an act is the most rudimentary form of a neurosis, so that the compulsive state is the first recognizable neurosis in a child. Later the conflict becomes expressed in thoughts rather than in acts, the thoughts becoming obsessional. The repetitive obligatory acts that express the rudimentary neurosis may be directed to external objects, to the child's own body or to others' bodies. Some are efforts at direct instinctual gratification, others at substitute gratification. The repetitive mechanism may attach itself to one or more of the following aspects of any conflict: (1) the libidinal activity; (2) the indirect expression of libidinal activity; (3) the emotional reactions to a conflict. It thus creates difficulty in reactions to emotionally toned situations because it invites censure and punishment and causes feelings of guilt and anxiety. The choice of neurosis depends on the secondary factors which determine where the repetitive process shall focus itself. This explains the concept of fixation. The choice is also determined in the phase of the child's evolution in which the repetitive mechanism becomes inflexible. The fact that every neurosis is basically a rigid compulsion-obsessional condition does not invalidate either the libido or the traumatic theory. It helps to make a more reasonable classification, based on the factors on which the repetition has been focused: (1) the forbidden drives, as in a perversion; (2) the emotional reactions to the conflict, and (3) a constellation of symptoms.

Thus there will be three main groups: (1) those in which disturbances in mood are the most prominent symptoms; (2) those in which perversions are most prominent, and (3) those in which the secondary psychoneurotic symptoms are most prominent. Each of these groups will contain symptoms from the other two, as Kubie demonstrates in the following chart:

	Manifested Continuously	Manifested Intermittently or Alternatingly	Masked Continuously
Group 1:	Frank moods Anxiety Anger Depression Elation	Perversions " Psychoneurotic symptoms	Psychoneurotic symptoms Perversions
Group 2:	The various constellations of psychoneurotic symptoms	Perversions Moods	Moods Perversions
Group 3:	Perversions.....	Moods Psychoneurotic symptoms	Psychoneurotic symptoms Moods

PEARSON, Philadelphia.

CO-CONSCIOUS MENTATION. C. P. OBERNDORF, Psychoanalyt. Quart. **10**:44, 1941.

Coconscious mentation occurs when there are in consciousness two streams of thought flowing in different directions and concerned with different topics, both being subject to unconscious influences. The process has been experienced by most people; it is possible to listen to and understand a lecture, to plan a discussion of it and to note critically the reaction of the audience at the same time. Pathologically it occurs in some persons who complain of feelings of unreality and absence of emotion. Coconscious mentation becomes aggravated when the person is concerned over an immediate personal dilemma or is fatigued.

Pathologic coconscious mentation is of three types: (1) a conscious concomitant repetitive registration of another stream of thought with a meaningless, irrelevant content, (2) a secondary stream of conscious thought assuming a commentating, critical, allusive function toward the content of the first stream of thought, and (3) a secondary stream which is conscious but concerns itself with topics unrelated to the first stream of thought. This secondary train of thought has a time of origin in the person's life, is associated with his superego functions and seems to protect his psychic economy against feelings of guilt and anxiety. Since it occurs in people who suffer from depersonalization, Oberndorf believes that the psychopathologic process in the two conditions is the same and cites 3 cases to prove his thesis. He suggests that the psychopathologic situation in both coconscious mentation and depersonalization is as follows: If through identification a man acquires a feminine as well as a masculine superego, he will have to repress the feminine superego after adolescence because it cannot satisfy his ego needs. This repression causes the patient to feel that he is not himself and that his masculine personality does not exist. The repressed superego may return under the guise of the secondary train of thought, either directly or as a way of avoiding the ego-dystonic feminine superego. The conflict between the masculine and the feminine superego hampers the patient's ego functions tremendously, but the coconscious mentation (the expression of the feminine ego-dystonic superego) defends the patient against feelings of guilt and anxiety for his masculine ego-syntonic desires.

PEARSON, Philadelphia.

PREDISPOSITION TO ANXIETY. PHYLLIS GREENACRE, Psychoanalyt. Quart. **10**: 66, 1941.

This paper deals with a discussion of the psychoanalytic theories of anxiety and seeks by the use of reported data on the results of experimental observations to reach conclusions as to why certain persons cannot subject their anxiety to psychic control. Greenacre discusses first Freud's reply to Rank's theory that the trauma of birth is the sole etiologic factor in the neurosis, a concept which does not take into account the constitutional factor. She asks whether Freud considered the possibility that the fetus may suffer discomfort and danger and may react to these by the use of reflex patterns without any psychic content, in other words, that a preanxiety pattern may develop as the result of fetal experiences. She cites Watson's observations on emotional reactions in babies and asks whether the causes of early fear reactions, that is, removal of support and loud sounds, are not conditioned by disturbances during intrauterine life and whether the rage reactions are conditioned by the trauma of birth.

It is interesting, also, that certain boy babies have erections at birth, and this fact might be correlated with the evidence that in early infancy erections may be caused by general tension resulting from difficulties in feeding. Hence their occurrence shortly after birth may be the result of intrauterine dissatisfactions. Also, premature infants show more anxiety reactions than do full term children. All of these observations induce the author to ask whether disturbances during intrauterine life may not cause organic tensions which deepen reflex response reactions and tend to accentuate reflex patterns of acceleration of physiologic processes which will later be associated with the psychic content of anxiety.

If this is so, the child will be born with a predisposition to anxiety reactions which become associated with the psychic content of anxiety as a result of the birth process, so that he has greater difficulty dealing with postnatal anxiety-producing situations. The greater liability the child has to experience excesses of anxiety the greater will be an excess of narcissism and the lesser the ability to adapt to reality.

Greenacre states that she realizes she seems to be only dusting off the theory that birth trauma is the cause of the neurosis and adding to it a concept of disturbances in fetal life. She does not regard the intrauterine state as the cause of neuroses, which are the result of a number of postnatal experiences, but she feels that in cases of severe disturbance the question of prenatal anxiety patterns should be considered.

PEARSON, Philadelphia.

A CASE OF STUTTERING. ELSE HEILPERN, Psychoanalyt. Quart. **10**:95, 1941.

Heilpern reports the analysis of a 21 year old man who suffered from a moderate degree of spasmodic stuttering. The analysis revealed that the patient had many infantile sexual impulses, such as marked anal erotism, respiratory erotism and oral erotism. The main impulses in his object relations were sadism and exhibitionism. He had a very strong fixation on his mother.

He preferred masturbation to intercourse, a fact which indicates that he either had never reached the stage of genital primacy or had regressed from that stage. All his sexual desires were restrained by strong fears of castration and death. The satisfaction of his masochism furnished the strongest secondary gain from his illness.

He seemed to have an innate disposition to libidinize sound. This disposition was increased by the association of sound with the primal scene. His stuttering followed speechlessness caused by the loud explosion of a toy torpedo at the age of 4, and this experience followed closely a primal scene. This speechlessness was the point of displacement from anal sadistic desires to the erotized speech function. At the same time, the mechanism of self punishment was established according to the equation: sharp noises = sexuality = death. In his unconscious, he treated words like "flatus" and "feces." In his fantasies he used speech for killing,

and he masochistically punished himself by the repressions and symptom formations in his speech. The analytic material in this case conforms to the requirements laid down by Fenichel for the analytic criteria of the causes of stuttering.

PEARSON, Philadelphia.

NESCIENCE, SCIENCE AND PSYCHO-ANALYSIS, M. F. ASHLEY-MONTAGU, Brit. J. M. Psychol. **18**:383, 1941.

This article is a reply to Roheim's contention that nescience of physiologic paternity among Australian aborigines is due not to failure of their sciential processes but to repression of a previously conscious knowledge of the relation between coitus and childbirth—this because of an unconscious hostility between father and son, an aspect of the Oedipus complex. Ashley-Montagu cannot agree on the basis of existing evidence that the Oedipus complex is of universal distribution, even within western culture, and he points out that it certainly has not been demonstrated in various primitive cultures. He concludes from the evidence presented that the Oedipus complex is of a nonbiologic nature, that it owes its origin to cultural factors and that it arises only under certain conditions, which are absent in many primitive societies.

The author devotes some space to a discussion of the relation of psychoanalysis to anthropology, presenting the view that a method and theory of mind based on the study of Europeans cannot safely be applied to cultures and minds differently organized, until repeated scientific experimental testing proves its validity in the new setting.

Among Australian primitives coitus is believed to be a factor in childbirth, but not the cause of conception. Children come from a spirit source independent of the bodies of a particular man and woman. Thus, while social paternity and maternity are important, the physiologic implications are not recognized. The author feels the adult beliefs are an extension, rather than a suppression, of childhood notions of procreation.

ALLEN, Philadelphia.

Diseases of the Brain

PERSONALITY DISORDERS WITH BRAIN TUMORS. MARK KANZER, Am. J. Psychiat. **97**:812 (Jan.) 1941.

Kanzer investigated the mental status in 205 verified cases of tumor of the brain and found the usual wide range of psychiatric symptoms. In very few cases did he fail to demonstrate a psychic disorder. On the basis of preoperative observations the cases were divided into four groups: (1) gradual development of mental symptoms, (2) marked personality disorders resembling dementia paralytica, (3) rapid course with severe disruption of personality and (4) the terminal phase of somnolence or stupor. Kanzer found the gradually developing symptoms present in cases of slowly growing and relatively benign tumors, whereas the acute symptoms were present in cases of highly malignant tumors or of those so situated as to interfere with cerebrospinal fluid circulation; such tumors also gave rise by transient blockage of the spinal fluid to episodic symptoms.

Kanzer pointed out that the mere cataloguing of mental symptoms in these cases is of little avail, but that the behavior of the individual subject should be considered from the viewpoint of his efforts to preserve his psychic integrity. The clinical picture was found to be dependent on the regional localization of the lesion, the degree of pathologic change and the premorbid personality.

Kanzer recommended separating specific disturbances (e. g., aphasia) from the general disturbances (e. g., confusion) and carefully studying the latter.

FORSTER, Boston.

THE INFLUENCE OF VISUAL AND AUDITORY STIMULI ON THE ELECTROENCEPHALOGRAPHIC TRACING OF PETIT MAL. ROBERT S. SCHWAB, Am. J. Psychiat. **97**:1301 (May) 1941.

Schwab has previously reported that in petit mal attacks the reaction time to visual stimuli dependent on incandescent lamps was prolonged or absent. This had been open to dispute because of the time required for an incandescent lamp to attain maximum brilliance. Schwab therefore studied the reaction time during petit mal attacks to auditory stimuli (compressed air whistle) and to visual stimuli arising from a neon bulb, which attain maximum frequency in a negligible period.

Schwab confirmed his previous observation that the reaction time is prolonged or absent. Moreover, he noted a terminating influence of the visual stimuli, so that attacks of shorter duration (six to seven seconds) were found to be terminated in three to five seconds. Longer attacks (ten to twenty seconds) were not affected. Auditory stimuli were found to have a greater terminating ability.

The author has described six degrees of petit mal epilepsy depending on the temporal duration of the attack and the terminating influence of visual and auditory stimuli. It is suggested that measurement of the reaction time may be of use in determining the effect of anticonvulsant therapy in petit mal epilepsy.

FORSTER, Boston.

THE CLINICAL VALUE OF HALLUCINATIONS IN LOCALIZING BRAIN TUMORS. SIDNEY TARACHOW, Am. J. Psychiat. **97**:1434 (May) 1941.

Tarachow studied 458 cases of verified supratentorial tumors of the brain and found hallucinations in 96. Hallucinations were classified as auditory (formed or unformed), visual (formed or unformed), olfactory, tactile and gustatory. Unformed auditory hallucinations were the most common, followed by unformed visual and then by olfactory hallucinations.

Tarachow studied the material from two points of view: (1) types of cerebral lobe involvement associated with each form of hallucinations, and (2) types of hallucinations associated with each form of cerebral lobe involvement.

The clearest localization was afforded by formed auditory hallucinations, which were primarily due to involvement of the temporal lobe. Lesions of the parietal lobe gave rise to a wide variety of hallucinations but showed a high incidence of the tactile type.

Tarachow concluded that although a certain type of hallucination may tend to arise from a lesion of a certain lobe, involvement of an adjacent lobe may yield the same type of hallucination.

FORSTER, Boston.

FRONTAL LOBECTOMY FOR BRAIN TUMORS. B. STOOKEY, J. SCARFF and M. TEITELBAUM, Ann. Surg. **113**:161 (Feb.) 1941.

Stookey and his associates discuss their observations on frontal lobectomy for glioma of the frontal lobe in 11 patients, 3 of whom had glioblastoma and the others astrocytoma. All the patients survived the operation, and, with the exception of the 3 who had extensive glioblastoma, all are alive and carrying on useful lives. In 6 of the patients with astrocytoma the authors were able to excise the tumor completely and, they hope, effect a cure. In the others the tumor extended beyond the line of excision, either dorsally into the motor area or across the midline into the corpus callosum. These patients have shown some improvement and have made fair social adjustments. More thorough and painstaking clinical studies are essential to detect absence of the frontal lobe after its removal than are necessary to determine the presence of a tumor of the frontal lobe. The frontal lobes are primarily association centers receiving impulses from all other parts of the brain. They are so connected that the proper function of each is dependent on impulses of a certain order and frequency reaching it through the association paths between the two lobes. The study of the 11 patients consisted of a complete neurologic examination on admission to the hospital and follow-up studies

by social workers at regular intervals. The conclusion was reached that the patients who had complete excision of the lesion, whether from the dominant or from the nondominant hemisphere, were intact with regard to their past and present life. They appeared genuine in their responses, and on nonpsychiatric investigation it would be exceedingly difficult to detect that anything had been wrong. Several of them functioned on a better level than before operation. They showed little impairment of general intelligence, planned and executed household duties competently and were able to sew, market, cook and plan for guests and the like. The common everyday performances were not slowed up. In some instances lack of distractability was notable. There was no hesitation in putting into effect a decision, and the decision once made was maintained until executed. There was complete return of the former emotional tone. Frigidity developed in only 1 patient. Some of the patients showed distinct evidence of new ability to learn. None showed any loss of inhibition or any spatial disorientation. Among the patients in whom the tumor extended beyond the line of incision the results were different. The patients were shallow emotionally, listless, indifferent and lacking in initiative. Three of the patients were able to care for their homes and children and to adjust themselves mentally if no complex situation arose. They were able to talk intelligently with one or two persons but were unable to carry on a conversation with a number of people or in a crowd. The cases offer confirmatory evidence for the theory that when the lesion was completely removed the intact lobe freed from the distorted impulses due to disease of the opposite side proved able to carry on for all practical purposes as efficiently as before. On the other hand, when only partial removal was effected, though there was some improvement, an irritant still remained which interfered with synchronous function of the two lobes.

J. A. M. A.

Intracranial Pathways of Infection from Diseases of the Sphenoid and Ethmoid Sinuses. Rudolph Kramer and Max L. Som, Arch. Otolaryng. **32**:744 (Oct.) 1940.

Infection from the sphenoid and ethmoid sinuses is not usually evident on gross examination but is frequently found if careful serial sections and bacteriologic studies are made. For the last seven years such studies have been made on a sinus block consisting of the sphenoid sinus, the basisphenoid bone, the ethmoid, the labyrinth and the cribriform plate, including the superior and middle turbinates. The block is decalcified and cut in serial coronal sections. Infection from the accessory sinuses occurred by direct lymphatic or venous extension, dehiscence and metastasis. In serial sections spread was noticed by osteomyelitis and osteitis, lymphatic extension along the nerves and the blood vessels, extension by way of the blood vessels to the cavernous sinus, direct invasion through dehiscences and spread through a persistent craniopharyngeal pouch. Hunter, Philadelphia.

Lead Encephalopathy in Children and Adults. A. J. Akelaitis, J. Nerv. & Ment. Dis. **93**:313 (March) 1941.

Akelaitis made a clinicopathologic study of lead encephalopathy in 3 children, 2 of whom died, and in 2 adults, 1 of whom died. The postmortem study suggests that the structural changes in children and in adults are a result of edema with exudation and hyperplastic changes in the leptomeninges and endothelial cells of the blood vessels. However, in children the process is apparently more severe, and the meningeal hyperplasia may lead to hydrocephalus. The lesions may vary with the duration of the intoxication before death occurs. The clinical picture in children is analogous to that of conditions in which the intracranial pressure is increased. The prognosis is grave, and residuums are frequent if the child survives. The clinical picture in adults is analogous to that of any severe cerebral intoxication.

J. A. M. A.

PSYCHOGENIC MANIFESTATIONS IN THE CLINICAL PICTURE DUE TO ATROPHY OF THE BRAIN. WILHELM RÜSKEN, Ztschr. f. d. ges. Neurol. u. Psychiat. **169**:637 (June) 1940.

Psychogenic complaints can be the initial symptoms of organic disease of the brain. Rüsken believes that these neurotic symptoms are due to the pathologic process. As a result of the alterations within the brain various inhibitory processes are interfered with, resulting in the ready appearance of psychogenic reaction patterns. In many of these cases, as the organic disease becomes more severe, the psychogenic features recede. The author reports 4 such cases in which the complaints followed trauma to the head and various psychogenic complaints were observed. In none of them were focal phenomena demonstrable. Headaches, functional tremors, hysterical weakness of a limb and defects of gait were all present. The author emphasizes the frequency of pseudodementia, such as is usually seen in cases of the Ganser syndrome. These mental changes are at times so bizarre as to arouse the suspicion of malingering. Encephalographic examination in all 4 cases gave evidence of atrophy of the brain. The author believes that the cerebral change resulting in this atrophy was the cause of the psychogenic manifestations. None of the patients had cerebral vascular disease. There was no evidence in any of the cases of premorbid personality defects or of psychopathic tendencies. There is no evidence that the trauma to the head merely released preexistent morbid tendencies.

SAVITSKY, New York.

OCCURRENCE OF ASEPTIC COMPLICATIONS IN CENTRAL NERVOUS SYSTEM IN SCARLET FEVER. H. C. A. LASSEN and J. BANG, Nord. med. (Hospitalstid.) **8**:2130 (Nov. 23) 1940.

Lassen and Bang report that of 9,826 cases of scarlet fever treated at the Blegdam Hospital from 1934 to 1940, 20 (0.2 per cent) presented symptoms of complications in the central nervous system. There was an increased number of cells, predominatingly lymphocytes, in the spinal fluid in all cases; in 6 cases the pleocytosis was the only sign of the disorder of the central nervous system. In 10 there were clinical signs of meningitis without focal symptoms; in 4 there were focal symptoms. The prognosis was good in all cases. The complications are ascribed to a virus infection, which is, however, not believed to be of "poliomyelitic" type, although 16 of the cases occurred from August to November. The authors found no demonstrable correlation between the occurrence of these aseptic infectious disorders of the central nervous system and scarlet fever with neurologic symptoms.

J. A. M. A.

PEDUNCULAR BRAIN STEM SYNDROME. K. KRISTIANSEN, Nord. med. (Norsk mag. f. lægevidensk.) **8**:2241 (Nov. 23) 1940.

A man aged 53 had had hemianopic disturbances in vision of migraine-like character which set in many years earlier, then symptoms, at first transitory, of a disturbance which, viewed in retrospect, is assumed to have been the first manifestation of the lesion in the right dorsorostral part of the brain stem. Kristiansen says that dissociated loss of sensibility, hyperpathia and spontaneous pain indicate that the thalamus must also have been affected somewhat early in the course. The last ten or twelve years of the patient's life were marked chiefly by epileptiform manifestations, diplopia as the result of paralysis of the oculomotor nerve, first on the right side and later also partly on the left, grotesque involuntary movements in the left upper extremity preeminently appearing as hemiballism and, finally, disturbing sensory phenomena on the left side. About the time of the onset of the peduncular symptoms the patient, formerly silent and taciturn, became talkative and cheerful. Death was due to bulbar symptoms. There was a crossed syndrome referable to the brain stem, distinguished from the ordinary vascular hemisyndrome by the extension of the lesion to the other side of the middle line. The author finds that the postmortem establishment of an expansive process in the form of

a cavernous hemangioma justifies one in not accepting a purely vascular genesis in such cases but in considering the probability of a neoplasm. The hemiballism was due to a lesion of the subthalamus. With regard to the psychic changes which may appear in patients with disorders in the rostral part of the brain stem, the tendency to affective instability is stressed. To what extent the migraine-like symptoms in the case were connected with the lesion of the brain stem is uncertain.

J. A. M. A.

PATHOGENESIS OF EPILEPTIC ATTACKS. A. FAURBYE, Ugesk. f. læger **102**:419 (April 25) 1940.

Faurbye states that the spasm threshold determines the development of spasms. Alkalosis, hyperhydration, hypoxemia, hyperlecithinemia and hypoglycemia increase the frequency of attacks in all cases of epilepsy by increasing the irritability of the nervous system. The complex spasm threshold is made up of these factors and several others. In some cases one factor is of special significance, in other cases another; in some it is perhaps a single factor, in others it is several factors simultaneously. In a group of cases in which daily spontaneous absences occurred the author found the most important factor to be the reaction of the blood, particularly the alteration of the reaction in an alkaline direction, and in 2 cases the intracranial pressure plus an unknown factor influenced by insulin was especially significant.

J. A. M. A.

Diseases of the Spinal Cord

OBSTETRIC EXPERIENCES OF WOMEN PARALYZED BY ACUTE ANTERIOR POLIOMYELITIS. S. KLEINBERG and T. HORWITZ, Surg., Gynec. & Obst. **72**:58 (Jan.) 1941.

Kleinberg and Horwitz determined the effect of acute anterior poliomyelitis on 243 women who had subsequent pregnancies. They examined 44 of the women, and the data on the remaining 199 were obtained through questionnaires filled out by the attending obstetrician and orthopedic surgeon and in some instances by the patient. In the series there were 13 women whose pregnancy was complicated by an acute attack of anterior poliomyelitis. Asymmetry of the pelvic inlet was found among approximately 80 per cent of the women. The distortion was usually mild and did not produce dystocia. Pelvic asymmetry was absent in those who because of extensive paralysis were completely bedridden, never having attempted to bear weight or to get about with braces and crutches. There were four main types of pelvic deformity: lateral pelvic obliquity, increased anterior pelvic tilt with exaggerated lumbar lordosis, anteroposterior axis deviation or rotation about a longitudinal axis and rotation of one innominate bone on the other about a transverse axis or torsional deformity. From 15 cases reported in the literature, 1 case reported to them and the 13 cases collected by them the authors conclude that pregnancy complicated by acute anterior poliomyelitis may be anticipated to progress normally, with a normal termination of labor and with normal offspring. The involuntary contractions of the uterus and the ability of the uterus to expel its contents spontaneously, also observed in patients paralyzed by tumor of the cord, spondylitis or vertebral fracture, are due to the fact that the uterus has an independent nerve supply and will contract after the spinal cord is transected and after its sympathetic nerve supply is extirpated. There was no instance of intrauterine poliomyelitis among the 29 cases. The passive immunity of the offspring derived from the mother does not persist for long, as a few cases of acute anterior poliomyelitis in infants less than 1 month of age (earliest, 9 days) have been reported. Analysis of the 243 cases in which the patient became pregnant one year or more after an acute attack of anterior poliomyelitis reveals that a normal and uneventful pregnancy and labor with normal offspring may be anticipated. There is no indication for interruption of pregnancy, except those reasons that

would also be operative in cases of nonparalytic women. Cesarean section was utilized in a higher percentage (11.5) of the paralytic women than in a comparable nonparalytic series, but it is the authors' belief that in some instances it may not have been warranted and that therefore the percentage probably does not represent the true index of the need of cesarean section for paralytic women.

J. A. M. A.

SUBACUTE INFANTILE POLIOENCEPHALITIS ANTERIOR. A. GAREISO and J. P. KÄFER, Rev. neurol. de Buenos Aires **6**:1 (Jan.-March) 1941.

In a boy of 13, who had previously been healthy, there gradually developed bulbar palsies, affecting the lips, tongue and larynx, without involvement of sensation, the pyramidal tract, the cerebellum or the cerebral cortex. The blood and spinal fluid were normal. He died of bronchopneumonia seven months from the onset.

Autopsy revealed atrophy of the cells of the bulbar medullary nuclei and degeneration of the peripheral portions of the nerves springing from them, with minimal glial proliferation and no degeneration of the white matter.

Cases of such a condition are rare, but their existence should be recognized.

J. A. M. A.

Peripheral and Cranial Nerves

ACUTE RETROBULBAR NEURITIS AS A MANIFESTATION OF ACUTE LOCALIZED TISSUE ANOXIA. WALTER F. DUGGAN, Arch. Ophth. **25**:299 (Feb.) 1941.

Acute retrobulbar neuritis has been ascribed to many different conditions. Duggan believes that the cause is an acute vascular catastrophe in the optic nerve characterized by arteriolar spasm and increased capillary dilatation and permeability leading to localized edema, tissue anoxia and loss of function in the involved tissue. This opinion is based on a study of two series of cases, in 48 of which vasodilator drugs were not used and in 23 of which they were employed in treatment.

Duggan would like to substitute acute angiospastic neuropathy as a better term for acute retrobulbar neuritis.

SPAETH, Philadelphia.

RECENT EXPERIENCES WITH OPERATION ON THE FACIAL NERVE. R. C. MARTIN, Arch. Otolaryng. **32**:1071 (Dec.) 1940.

In 16 cases of paralysis of the facial nerve operation was performed, with 1 failure. Of the 15 cases in which the operation was successful, 4 illustrating various points are reported.

CASE 1.—The left facial nerve was injured after simple mastoidectomy on July 10, 1939. On Aug. 3, 1939, although it was still discharging, the wound was reopened and a 1.5 cm. graft of the sural nerve inserted and sutured. As an afterthought, and because the first graft seemed smaller than the trunk of the nerve, a second segment was carefully laid in parallel to and touching the sutured graft. The patient was discharged on August 23. The first signs of improvement were noted on September 9. On September 29 drooling had ceased, and on October 7 the eyes winked synchronously. On November 16 facial symmetry was restored in repose. This child showed the most rapid return of tone and motion of all the patients in the series. He was the youngest one operated on, his age possibly being a factor.

CASE 2.—The facial nerve was severed below the mastoid process on Feb. 22, 1938. On May 2, 1938 the ends, found after much search, were brought together with two fine arterial silk sutures. On Aug. 1, 1938 improvement was noted. In April 1939 the patient could close the eye and move the right side of the face well except the frontalis muscle. In October 1939 the frontalis muscle was reacting slightly. This is the only case in the series in which the frontalis muscle resumed

its function. This recovery may be accounted for by the end to end anastomosis and the early operation.

CASE 3.—The facial paralysis was caused by a bullet wound of the face on May 28, 1938. Operation was performed on July 19, 1938. The tip of the mastoid was found to have been injured by the bullet. The facial nerve was exposed along the facial canal. From the stylomastoid foramen to near the horizontal canal the nerve was dark. About 2 cm. of fibrous nerve tissue was removed, part of this being the low vertical portion of the nerve and part of it the portion lying in the soft tissue on the forward course of the nerve toward the parotid gland. Except for discoloration the nerve appeared to be normal below and above the segment removed. The bullet was found medial and slightly anterior to the foramen, in or near the jugular bulb. A segment from the right saphenous nerve was sutured in place with fine arterial silk. The wound was closed with catgut and the skin with clips. The patient was discharged in three weeks. He was not seen again until May 12, 1939, when he could close the right eye and move the right corner of his mouth. He stated, "My face to all appearances is normal."

CASE 4.—A 2 year old child suffered injury to the facial nerve during simple mastoidectomy March 5, 1937. On March 13 reoperation showed the nerve to be injured just below the horizontal canal. About 1 cm. of nerve was resected and a graft from the sural nerve inserted and sutured with arterial silk.

Although still inclined to the feeling that operation should be performed when the infection has cleared up, Martin notes that in 2 of these cases the wound was still discharging and that this apparently interfered in no way with the healing. Postoperatively the canal is never entered. Dressings are not used over the graft or suture line, nor are strong chemicals employed. In all cases grafts are sutured as accurately as possible. Loss of hearing is slight. The patient with the gunshot wound complained that "loud noises bothered him," a finding indicative of injury to the stapedius nerve. In almost all the cases the frontalis muscle fails to act. In 2 cases in which tic was present the disturbance has ceased entirely in one and is much improved in the other. It is probable that the facial tics will disappear in time.

HUNTER, Philadelphia.

LOW BACKACHE AND SCIATIC PAIN ASSOCIATED WITH SPONDYLOLISTHESIS AND PROTRUDED INTERVERTEBRAL DISK. H. W. MEYERDING, J. Bone & Joint Surg. **23**:461 (April) 1941.

To determine the incidence of low backache and sciatica among patients suffering from spondylolisthesis, Meyerding reviewed the histories of the 745 patients for whom such a diagnosis was made between 1918 and 1940. He found 80 patients, or 10.7 per cent, who were so afflicted. A much larger percentage of patients suffering from spondylolisthesis had vague referred pain and paresthesia of the buttocks, hips and thighs that were aggravated by activity. He believes that patients with spondylolisthesis are more likely to have a protruded intervertebral disk than are those with a more stable spinal column. Trauma was a definite factor in 43 of the 80 patients. In the author's opinion fusion of the lumbosacral region is desirable in those cases of spondylolithesis with symptoms of protruded disk in which the surgeon is unable to demonstrate the disk at the time of the operation. This fixation will prevent movement and slipping and additional symptoms of backache and sciatic pain. Cooperation of the roentgenologist, the neurologist and the orthopedic surgeon has made it possible to diagnose the condition accurately and to relieve patients whose ailment has heretofore baffled the diagnostic efforts of even the most skilled surgeons.

J. A. M. A.

SOME NEUROLOGICAL COMPLICATIONS OF SERUM THERAPY. A. R. THOMPSON and J. B. L. TOMBLESON, Brit. M. J. **1**:1015 (June 22) 1940.

Thompson and Tombleson were able to find in the literature 120 authentic cases in which neurologic complications followed serum therapy, more than half of which followed the prophylactic injection of tetanus antitoxin in young adults. The

syndrome consists of pain in the neck and shoulders about eight to fifteen days after administration of serum, followed by paralysis and rapid and intense wasting of the muscles supplied by the affected nerves. Other signs and symptoms include a general serum reaction followed by collapse, vomiting, possibly coma, hemiplegia, hemianesthesia and pleocytosis. The generally accepted theory concerning the pathogenesis of serum neuritis is the concept that perineural edema causes compression or ischemic paralysis of the nerve trunks. The prognosis is good, and because this complication is rare, the authors believe that serum should continue to be used as a valuable therapeutic measure.

The authors could find only 10 cases of neurologic symptoms following the injection of antiscarlatinal or antistreptococcus serum; they report 2 cases exhibiting symptoms referable to the nervous system following the administration of antiscarlatinal serum.

ECHOLS, New Orleans.

BELL'S PALSY AND HERPES ZOSTER. JOHN D. SPILLANE, Brit. M. J. **1**:236 (Feb. 15) 1941.

It is generally believed that Bell's palsy is caused by exposure to a cold draft, but there are other predisposing factors. Spillane states that serologic evidence supports the view that zoster infection is a probable, though uncommon, cause of Bell's palsy. He briefly describes an epidemic of herpes zoster during which 5 of the patients were placed in one ward at the same time. One case of combined trigeminal and geniculate zoster was encountered. Five days after facial herpes appeared, ipsilateral facial palsy was noted. This suggests that the herpes virus invaded both the gasserian and the geniculate ganglion. That no auricular or faucial herpes developed indicates that herpetic invasion of the geniculate ganglion can occur without cutaneous manifestation in the distribution of its sensory fibers. The hypothesis was further strengthened by the isolated occurrence of a typical case of Bell's palsy in the same ward as that in which the cases of herpes zoster occurred.

ECHOLS, New Orleans.

IRRITATIVE LESIONS OF NERVES. W. K. LIVINGSTON, Confinia neurol. **3**:193, 1940.

Livingston states that an incomplete lesion of a major nerve may result in more severe symptoms than does complete division, apparently because the injury acts as a source of persistent irritation affecting the function of the nerve, and occasionally that of an entire extremity. The patients suffer from pain and hyperesthesia which may be out of proportion to the original injury, and the pain may not conform to the usual distribution of the nerve. In addition, there are sometimes motor and trophic disturbances, which may be severely incapacitating. The author expresses the belief that the focus of irritation resulting from a partial injury may send impulses to the central nervous system to set up reflexes which, in turn, produce peripheral changes. These can sometimes be abolished by injections of a solution of procaine hydrochloride at the site of irritation.

DE JONG, Ann Arbor, Mich.

REFLEX TRIGEMINAL NEURALGIA ASSOCIATED WITH HEART DISEASE. P. CHRISTIAN and H. PEGURRI, Deutsche Ztschr. f. Nervenh. **150**:263 (May) 1940.

Christian and Pegurri report in detail 7 cases of trigeminal neuralgia associated with cardiac decompensation. In each case the distribution of the pain was in the left maxillary division. The heart disease was of various types—hypertensive, valvular, etc. In each of the 7 cases the neuralgia disappeared as soon as the decompensation was cleared up by appropriate therapeutic measures. The authors state that they have seen other cases which were similar to the 7 reported. They attempt to interpret their data in accordance with Head's theory of zones of referred pain.

BRENNER, Boston.

Society Transactions

ILLINOIS PSYCHIATRIC SOCIETY

CHARLES F. READ, M.D., *President*

Regular Meeting, April 3, 1941

Artificial Fever Therapy for Dementia Paralytica, with Electroencephalographic Studies. DR. A. E. BENNETT, DR. PAUL T. CASH and DR. CLARENCE S. HOEKSTRA, Omaha.

The accumulative experience of workers in treating dementia paralytica with artificial fever and chemotherapy indicates results superior to those with malaria therapy.

In a series of 50 private patients with dementia paralytica followed for three years (of whom 82 per cent had the mild or intermediate type), 56 per cent obtained a full remission, 34 per cent were improved and 4 per cent died. The serologic reaction of the blood became negative in 34 per cent and that of the spinal fluid in 63 per cent.

In a series of 79 patients with dementia paralytica in state hospitals (of whom 52.2 per cent had the severe type of the disease) 19 per cent had a full remission, 32.9 per cent were improved, 40.7 per cent were unimproved and 7.9 per cent died. The serologic reaction of the blood became negative in 15 per cent and that of the spinal fluid in 42 per cent.

Of these patients, 24 had had previous malaria treatment without obtaining a full remission, 13 were graded as having a mild or an intermediate form and 11 had a severe form of the disease. After artificial fever and chemotherapy 29 per cent of this group obtained a full remission and 42 per cent were not improved.

Of 15 patients with asymptomatic neurosyphilis, the average duration of whose infection was twelve years and who had practically all been resistant to previous vigorous chemotherapy, the positive serologic reaction of the blood was completely reversed in 46.6 per cent and that of the spinal fluid was reversed in 73.3 per cent, while only 6.6 per cent failed to show serologic improvement.

For each of 4 patients with early acute dementia paralytica the electroencephalogram was distinguished by diffuse marked involvement of the alpha rhythm and the appearance of many slow potentials.

Three patients studied before and after treatment in whom a clinical remission was obtained showed return to a nearly normal electroencephalogram immediately after treatment.

Of a series of 10 consecutive patients who failed to obtain a remission, 8 showed a definitely abnormal record and 1 a record on the borderline of normal after a period of from one to three years.

For 7 of the 15 patients studied, the disturbance of electrocortical function appeared to be most marked in the frontal leads.

DISCUSSION

DR. CLARENCE A. NEYMANN, Chicago: Two points are important in the treatment of syphilis with artificial fever produced by physical means. 1. Sufficient heat must be applied over an adequately long period. Dr. Bennett has already mentioned this. Bessemans has shown that a temperature below 103.5 F. is absolutely ineffective and useless in the treatment of syphilis. A temperature of 105.8 F. seems to be most compatible with adequate therapy. At this temperature the patient is not in danger of heat stroke. A robust man or woman can bear 105.8 F. for eight hours without any serious physical after-effect. 2. The patient should

receive adequate chemotherapy at the height of the fever, as Simpson, Bessemans and many others have advocated.

There is only one question. This concerns the mortality rate in the authors' series. It appears to be rather high, but it is probable that Dr. Bennett has been overly honest. Although my associates and I have observed patients that have died some weeks or months after artificial fever therapy, there has not been a single death in Chicago directly attributable to this treatment since 1932. During the entire time we have employed artificial fever, now over twelve years, we have experienced only 2 deaths resulting from its use. Up to Jan. 1, 1938 reports on about 967 patients suffering from dementia paralytica who had been treated with artificial fever in the various clinics in this country and abroad had appeared in the literature. The mortality rate as a direct consequence of artificial fever therapy was less than 2 per cent. I understand from Dr. Walter Simpson and others that there have been practically no deaths resulting from artificial fever in recent years. Naturally, some patients with dementia paralytica have died because the disease was not arrested.

Dr. Victor Gonda, Chicago: I have missed any reference in the authors' paper to the typhoid-paratyphoid fever treatment of dementia paralytica. This is surprising, as in the United States this form of artificial fever therapy seems to be the method of choice. It is much easier on the patient and does not have the mortality of the malaria treatment, even though the latter is carried out with the utmost care.

Dr. Charles F. Read, Elgin, Ill.: It is now quite generally the practice to combine chemotherapy with hyperpyrexia. Has any one run control treatments with hyperpyrexia and without chemotherapy? At one time physicians were excited over the use of tryparsamide without fever therapy, and a considerable number of remissions were obtained with use of this drug alone. Now, in the discussion of fever therapy, the method seems to be neglected.

Dr. Roy Grinker, Chicago: I have been asked to discuss the electroencephalographic changes. It is obvious in Dr. Bennett's cases that in the actual psychotic state the alpha rhythm disappears and two types of waves appear: the so-called beta waves, with a frequency of about 25 per second, and the delta rhythm, which is much slower, perhaps 2 or 3 per second. It is recognized that interpretation of the electroencephalogram is fraught with great difficulty. First, there is a great variation among so-called normal persons, and, second, the number of possible artefacts is tremendous. This observation of Dr. Bennett and his associates seems to be consistent with the results of others. The fact that after treatment the so-called alpha rhythm, which is normally found in healthy persons, reappears indicates that the damage to the nerve cells whose spontaneous beat gives rise to the electric potentials visible in the tracings is not permanent and that the cells are not destroyed but perhaps suffer temporary disturbance of function. I wonder whether it is not possible to correlate the type of pathologic rhythms that have been seen here with particular clinical phenomena appearing during the psychosis. For example, were fast waves predominant in persons displaying greater excitement and the slow waves in those who were more stuporous or lethargic? It seems that, in the presence of a disease process which temporarily throws cortical tissue out of function, two very different types of waves are substituted for the normal, and that by using them as polar opposites they might possibly be correlated with some type of opposition in the clinical syndrome. Obviously, the electrical potentials in cases of organic disease of the brain do not in themselves indicate degeneration of the tissue; they may mean simply a functional disturbance and therefore are not indicative of a bad prognosis.

It has been interesting to observe this careful piece of work, and one hopes that further studies will clear up some of the questions raised.

Dr. A. E. Bennett, Omaha: With regard to Dr. Gonda's question why we have not used tryparsamide with artificial therapy: We decided not to use tryparsamide because other workers were employing it and we were anxious to try out

other arsenicals. We used bismarsen at first; later we changed to mapharsen. Recently we have been using a newer drug, called aldarsone (the formaldehyde sulfoxylate of 3-amino-4-hydroxyphenylarsonic acid).

As to the question of mortality: We have followed the cooperative clinical group method of calculating immediate mortality, deaths within three or four months, and of delayed mortality, deaths within three years. The state hospital series gives a mortality of 8 per cent with artificial fever therapy. In a series of private patients only 2 died during treatment and 1 two years after treatment.

I agree with Dr. Grinker's statement that most electroencephalographic records require careful interpretation because of normal variation; certainly, a larger series of cases is needed before one can draw any positive conclusions. I think we can rule out artefacts with our method. I feel certain that we can recognize them.

Dr. Read asked whether any patients were treated with hyperpyrexia alone, as a control for patients given chemotherapy and hyperpyrexia. I am not very familiar with such experiments. Dr. Walter Simpson first used stfaight fever therapy for early syphilis and found that there was a tendency to relapse and recurrence; he quickly abandoned the method when he discovered the advantage of adding chemotherapy. A combination of the two types of treatment gives better results in the end, but I cannot state whether artificial fever therapy alone would compare with malaria therapy alone. I think Dr. Neymann could answer that question better than I.

Chronic Alcoholism at the Cook County Hospital. Dr. Josephine M. Chapin and Dr. William M. McGaughey, Chicago.

Statistics on the incidence of alcoholism at the Cook County and Psychopathic Hospitals are presented and compared with those of other institutions.

At the Cook County Hospital 1,333,000 patients were admitted in the past forty years. For 19,000 of these alcoholism was the major diagnosis. To the Cook County Psychopathic Hospital in the past twenty-five years 130,000 patients have been admitted, of whom 24,000 had chronic alcoholism.

Graphic representations of the incidence of alcoholism at Cook County Hospital show a peak incidence in 1912, followed by a low incidence from 1914 to 1919. A marked increase from 1920 to 1922 was then followed by a general decrease up to 1933 and an increase in 1937, the incidence having not yet reached previous high levels.

At the Psychopathic Hospital the admissions for alcoholism were low from 1918 to 1920, followed by a marked increase from 1921 to 1924. From then, there was a gradual slight decrease until 1935, with a secondary rise from 1936 to 1940.

In comparing this incidence with that reported from other hospitals, it was noted that all the figures show a low rate of admissions for alcoholism in 1920 and the immediately preceding years. This low incidence was followed by a striking rise from 1922 to 1924 in all the hospitals reviewed. In the later years of prohibition and the early years of repeal there is no striking or consistent variation.

DISCUSSION

Dr. Charles F. Read, Elgin, Ill.: In California they have an "Alcoholic Inebriate Act," by which alcoholic persons may be committed for a period of two years. They may be paroled by the institution or by the colony to which they are sent, but they are not discharged under two years except by action of the State Department of Mental Health. Whether that provision does much for them I do not know. I could say much concerning the attitude of state hospitals toward alcoholic persons. The hour is too late for that, except to confess to a certain amount of exasperation in the face of the inadequacy of treatment in these hospitals. It seems that these patients should be able to do something for themselves and that the state institutions should do more for them.

DR. ALEX ARIEFF, Chicago: Because the Municipal Court of Chicago Psychiatric Institute is intimately concerned in certifying some of these patients, it may be of interest to give a few figures from 1931 to 1939. In 1930-1931 160 alcoholic persons were certified, or 11 per cent of all the patients seen at the Psychiatric Institute. Thirty-five per cent of all the patients were certified, which means that in 1931 about one third of all psychotic patients were alcoholic. In 1932 there were 2,038 patients; 12 per cent of these were alcoholic and 30 per cent of all the patients were certified to Cook County Hospital. In 1940 there was a slight increase in the number; 2,287 patients were seen at the Psychiatric Institute, of whom 373, or about 17 per cent, were certified and 250 who were alcoholic were not certified; in that year 31 per cent of the total were certified. In other words, over half of the patients certified to Cook County Hospital were alcoholic. Every alcoholic patient with or without a psychosis, whether deteriorated or not, presents a problem. Some have been seen three or four times in the hospital and have been in the Institute many times, even in Bridewell.

DR. JOSEPHINE M. CHAPIN, Chicago: The graphs were made on semilogarithmic paper in order to compare the relative yearly incidence in institutions of different sizes.

A Case of Schizophrenic Insight. DR. CARL-GUSTAF D. TILLMAN, Topeka, Kan.

NEW YORK NEUROLOGICAL SOCIETY AND SECTION OF NEUROLOGY AND PSYCHIATRY, NEW YORK ACADEMY OF MEDICINE

LEON H. CORNWALL, M.D., *President, New York Neurological Society, Presiding*
Joint Meeting, May 6, 1941

Neoarsphenamine Encephalitis with Recovery. DR. E. D. FRIEDMAN and DR. ERNEST NEWMAN (by invitation).

A 28 year old man was admitted in stupor to the Beth Israel Hospital, to the neurologic service of one of us (E. D. F.). A routine physical examination by his family physician two weeks prior to admission revealed only that the right pupil was larger than the left but reacted well to light and in accommodation. The Wassermann reaction of the blood was positive. This was the first time the patient was aware that he had syphilis. Antisyphilitic treatment was instituted. He received a weekly intramuscular injection of 0.2 Gm. of bismuth subsalicylate in oil for five weeks. This was followed by an intravenous injection of 0.3 Gm. of neoarsphenamine. There was no untoward reaction.

One week later, that is two days before admission, the patient was given his second dose of neoarsphenamine (0.45 Gm.). The following morning he complained of chilly sensations but was able to go about his work. On the subsequent day, while dressing in the morning, his wife noticed him staring into space with what she described as a queer expression. This was followed by generalized convulsions, associated with projectile vomiting of "coffee ground" material. This lasted ten minutes, and the patient then lapsed into stupor. He was admitted to the hospital in this condition.

Physical examination on admission revealed an extremely pale man in acute distress. He lay on either his right or his left side with one of his knees flexed on his abdomen in a fetal attitude and resisted vigorously any attempt to change his position. There was urinary and rectal incontinence. Respirations were rapid (38 per minute) and irregular. The pulse was 110, and the blood pressure was 112 systolic and 70 diastolic.

The patient was uncooperative, making a thorough physical examination difficult. His heart and lungs were normal. His abdominal wall was rigid, but tenderness could not be elicited. Neurologic examination revealed diminution of the patellar reflexes. No pathologic reflexes were obtained. The fundi were normal.

Urinalysis revealed a 2 plus reaction for albumin, a few granular casts and 1 to 2 red blood cells per high power field. The blood count showed 6,200,000 red cells, 104 per cent hemoglobin and 26,000 white cells, with 90 per cent neutrophils and no eosinophils. The sugar content of the blood was 166 mg. per hundred cubic centimeters, and the nonprotein nitrogen was 36 mg. The spinal fluid was removed under normal pressure. Microscopic examination revealed 16 white cells (11 lymphocytes and 5 neutrophils) per cubic millimeter. The sugar content of the spinal fluid was 40 mg. and the total protein 70 mg. per hundred cubic centimeters.

Course in the Hospital.—The temperature on admission was 99 F. and rose rapidly to 104 F. on the night of admission. Associated with this the patient presented a picture of extreme restlessness and stupor. Therapy consisted in the administration of 1 cc. of epinephrine hydrochloride (1 : 1,000) every three hours intramuscularly and of 250 cc. of a 50 per cent solution of dextrose intravenously, a clysis of saline solution and sedation.

By evening of the second day his temperature fell to 100.4 F. In spite of this, he was still stuporous and extremely uncooperative. The blood sugar at this time was 120 mg. per hundred cubic centimeters.

On the morning of the third day in the hospital, the patient was rational for the first time and, except for complete amnesia for the two previous days, seemed to be perfectly well. This was the first time a satisfactory neurologic examination could be performed. His right pupil was larger than the left and reacted more sluggishly to light. The fundi were normal. The deep reflexes of the upper extremities were active. The left knee and ankle reflexes were more active on the left than on the right. The rest of the neurologic examination gave negative results.

He remained in the hospital for four weeks, during which time his only complaint was mild headache and dizziness. The change in his clinical status was associated with disappearance of the abnormal elements in the urine. The blood count became normal except for persistent eosinophilia (7 per cent). This was not explainable by the presence of ova or parasites in the stool or by any history of allergy.

Examination of the spinal fluid two weeks after admission revealed normal manometric and chemical values. The Wassermann reaction of the spinal fluid was strongly positive, and the colloidal gold curve was 123310000. There were 2 lymphocytes per cubic millimeter. A series of gastrointestinal roentgenograms, performed because of the presence of blood in the patient's vomitus on admission, revealed a duodenal ulcer. On discharge the patient felt perfectly well.

During the eleven months following discharge the patient received weekly injections of 2 cc. of 10 per cent bismuth subsalicylate in oil. With this he took on the average 30 minims (1.85 cc.) of potassium iodide daily. At the end of this period, the Wassermann reaction of the blood was 1 plus and that of the spinal fluid was negative, and the colloidal gold curve became normal. The only neurologic abnormality at present is absence of the ankle reflexes. Both pupils react to light, but the reaction of the right pupil is more sluggish and irregular. Otherwise the patient is free from symptoms.

We feel that this case is one of encephalitis following the administration of an arsenical. Reports of 175 such cases have appeared in the literature, and our case resembles them except for the outcome. First, in this case the onset appeared after the second dose; this occurred in 50 per cent of the reported cases. The symptoms, including the acute onset, headache, vomiting, convulsions and stupor, described in the reported cases were also observed in ours. The transitory

abnormalities that we noted in the urine have been present in 46 per cent of the reported cases. The elevated white cell count of the spinal fluid was noted in 63 per cent of the cases.

The unusual features in this case were, first, the recovery from a condition which has a reported mortality of 76 per cent; second, the presence of 7 per cent eosinophils, which suggests that the reaction may be an allergic phenomenon, and third, the conversion of a positive Wassermann reaction of the spinal fluid to a negative one with what is usually considered inadequate therapy.

DISCUSSION

DR. BERNHARD DATTNER (by invitation): In the past two years I have had the opportunity of observing 4 such cases in Bellevue Hospital. In 1 case encephalitis developed during routine therapy with neoarsphenamine. The history and clinical findings were not unlike those in the case presented here tonight, and here, also, the patient survived. The other 3 cases were those of patients with early syphilis who had received massive doses of an arsenic compound. One of them died, and 2 survived.

There seems to be a difference with regard to the mechanism of the reaction between the patients who received routine treatment and those who had the massive dose. In the group who received routine injections some type of idiosyncrasy or hypersensitivity is apparently concerned, for the amount of arsenic received by these patients was much too small to account for the serious effects as judged by the usual standards of toxicity. All 3 patients who received massive doses of an arsenic compound (mapharsen) manifested the encephalitis within five to six days. As it is well known that large doses of arsenic may cause encephalitis, the condition in the latter group might fall under a purely toxic classification.

It is interesting, however, that in the 1 patient at Bellevue Hospital who died during therapy with massive doses of an arsenic compound the so-called ninth day arsenical erythema of Milian developed simultaneously with the onset of her cerebral symptoms. This reaction is a toxicoderma, associated with fever, nausea, vomiting and other symptoms. It has its onset on the eighth or ninth day after the first injection of an arsenical drug. It is encountered in less than 4 per cent of patients who receive one or more injections of an arsenical compound, and its onset is usually about two days after the second injection. The amount of the drug administered seems to have little influence on this reaction. In my patient both the encephalitis and the so-called ninth day erythema occurred eight days after the intensive treatment with mapharsen was started. The treatment lasted only six days. Since in half the cases of hemorrhagic encephalitis reported in the literature, as stated by Dr. Newman, and also in his case, the onset of the attack followed the second injection of an arsenical drug (which was made eight to nine days after the first), there may be some relation between the early acute arsenical erythema and hemorrhagic encephalitis.

The one significant laboratory finding in all the cases of hemorrhagic encephalitis which I observed was the increase in total protein in the spinal fluid. Presumably this is due to an increased permeability of the cerebral vessels, which might well explain the transitory positive Wassermann reaction of the spinal fluid in the case reported by Dr. Friedman and Dr. Newman. In the case of the patient who died at Bellevue Hospital the total protein was so increased that a coagulum formed in the spinal fluid. The Wassermann reaction of her spinal fluid also became strongly positive during the critical stage of her condition.

DR. ISIDORE MARGARETTEN: I had 4 cases of arsenical dermatitis in a series of syphilitic patients whom I treated with neoarsphenamine and a bismuth compound. All these patients recovered from the dermatitis, and in all instances the serologic reactions, both of the spinal fluid and of the blood, became negative after the dermatitis cleared up.

I should like to know what brought about the negative serologic reaction after the dermatitis and whether it is best to produce a mild toxic effect in order to bring about a negative serologic response?

DR. CHARLES DAVISON: The pathologic picture in these cases interests me. I have had an opportunity of observing several cases in which necropsy was done, and in practically all of them there was little involvement of the gray matter. The pathologic process consisted of minute hemorrhages, especially in the perivascular spaces, with demyelination. The most interesting feature was the vascular distribution of the lesions. The branches of the anterior cerebral, the superior cerebellar and the spinal arteries seemed to be chiefly involved. I should like to know whether other neuropathologists have had the same experiences.

DR. JOSEPH H. GLOBUS: I, too, was much impressed with the excellent results obtained in the case under discussion, but I was surprised that the term "encephalitis" has been used here so frequently in describing a pathologic process occurring in pericapillary encephalorrhagia due to neoarsphenamine. This, of course, is not an inflammatory disease of the brain. It is a degenerative process which affects primarily the blood vessels. The blood vessels seem to be rather sensitive to arsenic as well as to other heavy metals, which apparently accumulate in the vessel walls and increase their permeability; this, in turn, results in diapedesis from the affected blood vessels, leading to the formation of ring hemorrhages.

The smaller vessels are commonly involved in this disease. I have not been able to establish a preference for any system of vessels, as Dr. Davison did, but found the so-called terminal vessels in the corpus striatum, in the red nucleus and in the dentate nucleus, wherever vessels seemed to terminate blindly, most likely to be affected. Since the condition is a primary disease of the capillaries and precapillaries and the lesions are found about them, it is best described as pericapillary encephalorrhagia. Apparently in the instance reported it was not a pronounced extravasation, for the fluid was not xanthochromic and no red cells were seen in the spinal fluid. In the cases that I have studied red cells were found in the spinal fluid.

DR. BERNHARD DATTNER: There has been a great deal of discussion about why neoarsphenamine dermatitis reverses a positive Wassermann reaction; a plausible explanation is that one is dealing with a maximal therapeutic effect in which toxic manifestations occur; this means the patient received the maximal tolerated dose. Then, as pointed out by Erich Hoffmann (*Deutsche med. Wchnschr.* **45**:1233, 1919), esophylaxis may be involved in the serologic reversal. This means that the skin is cooperating in the defense against the spirochetes, forming what may be considered antibodies for combating the disease. Therefore Rajka and Radnai (*Ztschr. f. d. ges. Neurol. u. Psychiat.* **131**:674-705, 1931), in Budapest, Hungary, suggested that in all cases of Wassermann-fast syphilis the skin should be stimulated by irradiation with artificial sunlight. They reported a group of cases in which the Wassermann reaction had been persistently positive and became negative after irradiation with artificial sunlight. I am sure there must be many other explanations.

DR. ERNEST NEWMAN: I should like to suggest another possible explanation for the change from a positive to a negative Wassermann reaction of the spinal fluid; that is, the intense fever which the patient had (a temperature of 104 F. for two days) may have been responsible for the change.

DR. E. D. FRIEDMAN: We accept Dr. Globus' criticism; as a matter of fact, if he had not preceded me, I was going to say that the condition in this case is not encephalitis but pericapillary encephalorrhagia, as he prefers to designate it. One might explain these pericapillary hemorrhages on the same basis that Ricker, Schmidt and others explained small hemorrhages in the brain following trauma to the skull, namely, as vasomotor paresis with exudation of serum from the walls of the vessels and diapedesis of red blood cells. The mechanism in our case would be analogous to that described.

As a matter of fact, Berner, in a recent paper, grouped together all these small hemorrhages in the brain and said that they are not characteristic of any

particular condition but may be observed in many states, varying from trauma to the skull to anaphylactic reactions in the brain. This condition therefore may be a generic response of the blood vessels of the brain to toxic agents of all kinds.

Brain Abscess of Uncommon Origin: Relation to Osteomyelitis of the Skull (Clinicopathologic Study). Dr. Victor W. Eisenstein (by invitation), Dr. E. D. Friedman and Dr. Charles Davison.

Approximately two thirds of the cases of brain abscess arise from local infections about the head. While most are of otitic origin, about 10 per cent arise from other foci about the cranium, notably the paranasal sinuses and the soft tissues of the face and scalp. In this small group of cases osteomyelitis of the skull often appears as the intermediate step from extracranial to intracranial infection.

Involvement of the bones of the skull has been known to follow relatively minor infection. Swimming, with the aspiration of water into the nose, has been responsible for serious intracranial involvement, particularly in young persons. Furuncles of the face and scalp, peritonsillar abscess, sinal infection, minor injury of the head, and office treatment of the nasal sinuses, as well as radical operation on the sinuses have resulted in osteomyelitis of the skull, brain abscess and death. Wounds of the skull due to penetrating objects, particularly military injuries, have resulted in abscess of the brain. The intermediate role of osteomyelitis is often not apparent, since the lesion in the bone may be microscopic.

Nine illustrative cases are presented, the abscess in all instances arising from a local (nonotitic) infection about the head. In 2 cases the brain abscess followed peritonsillar abscess; in 3 cases the cranial and intracranial involvement was secondary to incised furuncles of the face; in 3 cases the complications were secondary to clinically mild sinal infection, and in 1 case a fulminating process followed swimming.

The pathogenesis of intracranial extension is discussed. The role of the diploic veins in the spread from a local septic focus is emphasized, and the venous pathways to intracerebral extension are illustrated. Search for minute or microscopic foci of suppuration in the skull is found to be advantageous in revealing the origin of the so-called cryptogenic abscess.

The clinical correlations include the interpretation of symptoms on the basis of pathogenesis of spread. Boggy abscess in the scalp (Pott's puffy tumor) occurs early and is a valuable clinical sign of osteomyelitis of the flat bones of the skull. The earliest roentgenographic evidence of bone involvement is to be found about the diploic channels. Early in the course of the process the spinal fluid shows no abnormality, except occasionally some increase in pressure. When brain abscess has developed, increased spinal fluid pressure and pleocytosis accompany the headache, drowsiness, fever, nuchal rigidity and focal neurologic signs which point to this complication. Early and radical removal of the affected bone and adjacent thrombotic areas in the diploe is suggested in the therapeutic implications of this study.

DISCUSSION

Dr. Joseph E. J. King: From the title one would believe that in all these cases the abscess was secondary to true, distinct osteomyelitis of the skull—osteomyelitis as it is generally understood. I think one should first differentiate between true osteomyelitis, i. e., inflammation of the myelium of the skull, and bone necrosis, such as necrosis of the bony wall about the lateral sinus, the posterior plate of the frontal sinus and the walls of the sphenoid. No doubt some vestige of osteomyelitis exists in any type of infection of the bone. Ordinarily, however, the term osteomyelitis of the skull does not include such diseases of the bone as mastoiditis, petrositis, necrosis of the dural plate about the sinus and the posterior wall of the frontal sinus. One might go further in differentiating between true osteomyelitis of the cranial vault and that of the basilar portion of the cranium, maxilla and mandible.

In the authors' series, case 1 was an instance of retropharyngeal abscess extending from below upward, producing osteomyelitis of the base with infection extending into the intracranial space and resulting in meningitis rather than a true abscess of the brain. In case 2 it was reported that the intracranial involvement followed a peritonsillar abscess with typical purulent meningoencephalitis, without mention of osteomyelitis. In case 3 the intracranial involvement followed true metastatic osteomyelitis of the skull secondary to old suppurative involvement in the pelvis. In case 4 the intracranial involvement followed a deep abscess in the preauricular region, but no mention was made of osteomyelitis. Case 5 was a typical instance of the "swimming episode," with typical osteomyelitis, evidenced by multiple Pott's puffy tumors and true osteomyelitis, as has been described by Mosher and others. This case is as typical as one of acute appendicitis. Case 6 was an instance of typical infection of the paranasal sinuses following a cold, with necrosis of the posterior plate of the frontal sinus, extradural abscess and subcortical abscess—a common occurrence. It is believed that one should consider the condition here "necrosis of the posterior plate" rather than true "osteomyelitis of the skull." This is the usual picture even in abscess of the frontal lobe.

Case 7 also is typical. In this instance a 14 year old girl had had bilateral mastoidectomy at the age of 3 years. Eleven years later there was a sudden flare-up on the left side. Before completing the reading of the clinical record, one could make the diagnosis of an old thrombosis of the lateral sinus with subsequent development of multiple abscesses. I have recently had just such a case. There is no question about there being necrosis of the bony wall of the lateral sinus, but I think this would hardly be called true osteomyelitis. In case 8 there was a history of infection of the upper respiratory tract, sore throat and pain over the right eye, with mucopurulent discharge from the right side of the nose. The findings were interesting. However, no mention was made of osteomyelitis of the skull. In case 9 the intracranial involvement evidently followed infection of the frontal sinuses, but there was no mention of osteomyelitis.

Therefore, only in cases 3 and 5 was there real osteomyelitis as one considers the word, notwithstanding the fact that in the other cases there may have been local necrosis of bone. At any rate, in the other cases there was no evidence of extensive osteomyelitis of the skull.

In the experience of my associates and myself the commonest sequela of true osteomyelitis of the skull is massive suppurative leptomeningitis, by which one means a large collection of pus, ¼ to ½ inch (0.6 to 1.2 cm.) thick in its central portion, overlying the cortex of the brain. This may be in conjunction with an abscess, but most frequently is not; in fact, out of about 70 cases of brain abscess, we have seen only 3 in which abscess followed true osteomyelitis of the skull. In 1 case it followed sequestration of the right supraorbital ridge, in which massive suppurative leptomeningitis occurred before operation; in another case multiple abscesses followed massive osteomyelitis of the right frontal and parietal regions, and in the third it followed traumatic osteomyelitis which involved the left mastoid.

The majority of deaths following osteomyelitis have been due to suppurative leptomeningitis without abscess formation.

I agree heartily with the authors that prevention of either one of these severe complications, i. e., abscess or suppurative leptomeningitis, can best be accomplished by early recognition of osteomyelitis of the skull and proper operative procedures for its removal.

In order to recognize osteomyelitis in its early stage one should make repeated roentgenographic examinations of the skull. If this is done, a definite area of decalcification can be seen about twelve days before the typical moth-eaten appearance is noticeable. The condition can then be dealt with adequately.

Although the commonest infection in the sinuses may be streptococcic, the organism recovered in cases of osteomyelitis is invariably Staphylococcus aureus. Therefore, sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) should be administered in cases of true osteomyelitis. We had an instance in which a

fatality would surely have followed metastases from various bones had it not been for the use of sulfamethylthiazol (2-[paraaminobenzenesulfonamido]-4-methylthiazole).

Dr. Edmund P. Fowler Jr. (by invitation): I should like to hear exactly what Dr. King means by "true osteomyelitis." Part of the difficulty in the understanding of this subject is due to differences in definition. "Clinically," only the acute progressive and extensive phase of osteomyelitis of the skull is generally recognized, and yet small microscopic, relatively inconspicuous areas in the temporal bone may after ten, fifteen or twenty years develop into abscess of the brain.

All air cells, whether in the nasal spaces or in the mastoid, abut on marrow spaces. Ordinarily marrow is very resistant to infection and does not become infected, but when it does the infection is hard to eradicate, whether in the skull or in a long bone.

In the paper this evening, Dr. Eisenstein purposely omitted discussing the 90 per cent of brain abscesses that come from infections of the ear. Unfortunately, my specialty is the ear; so I venture to show you some uncommon types of infections that originated from the ear.

(Slide) Here is a temporal bone in which operation did not go far enough, for in front of the superior canal was a small abscess which broke through and destroyed the dura. By direct extension it involved the brain.

(Slide) In this unusual case from the Manhattan Eye, Ear and Throat Hospital there were thrombosis of a sinus, involvement of the superior petrosal sinus and a thrombosed vein running forward into the frontal lobe, where an abscess developed.

The next slide shows a clot and large abscess secondary to thrombosis of the lateral sinus. One rarely finds an abscess of the frontal lobe arising from the ear.

(Slide) In this case the mastoiditis was so mild that the patient did not complain even of pain in the ear. He had catarrhal disease of the middle ear and terminal meningitis. Pathologic specimens show an area next to the dura which is considerably thickened and an air cell the entire drainage of which is along the dura. Air cells of this type occur all around the temporal bone. In practically every case of otitis media they become infected through the air cell system and drain through the vascular channels of the dura. It is strange that one does not have more trouble from this cause. The real danger is with chronic or repeated infection, for drainage through the middle ear becomes more difficult with each episode.

(Slides) These are of the temporal bone of a man who had chronic otitis media and dizziness for twenty years and in whom meningitis suddenly developed. Mastoidectomy revealed pus, but the patient died. This section showed that he had an area of low grade chronic osteomyelitis in front of the anterior vertical semicircular canal, measuring not more than 4 mm. in diameter. The dura became thickened. The abscess, however, broke through the bone into the semicircular canal, producing labyrinthitis, meningitis and death.

The new bone formation which one sees in the marrow in almost all cases of chronic otitis media with smoldering infection is the type one finds elsewhere in the body in cases of deep osteomyelitis. This, with edema, produces the decreased radiability which Dr. King says one will find in twelve or fourteen days, before any cavity formation is apparent in roentgenograms of the frontal bones. Decreased density usually occurs in the long bones or skull at about six weeks. Then, paradoxically, there is more new bone growth; so with these chronic infections the end result is increased density in the roentgenogram. Each step is part of osteomyelitis, and I agree with the authors that chronic osteomyelitis is just as important a factor in the formation of brain abscess as is acute osteomyelitis.

Dr. Joseph H. Globus: It is obvious that the paper is limited to what is commonly considered as "contiguous brain abscess," such as can be traced to a suppurative focus in adjacent tissues, particularly to an osteomyelitic process in and about the paranasal accessory sinuses. Among the several views expressed,

the concept of a retrograde venous thrombosis as the channel of infection was stressed. This view is held by many and is very likely a satisfactory explanation for the origin of many contiguous brain abscesses. It is not out of accord with the view which Horn and I expressed when we attempted to show that in a large number of cases of contiguous brain abscess circumscribed leptomeningitis takes place early in the disease process and from that point vessels, not always veins, carry the infection to the surrounding tissue, and not always into the depths of the white matter.

With this in mind, the first case reported here might be regarded as an instance in which the brain abscess could have developed in the course of time, but need not, however, be grouped as yet with cases of brain abscess, particularly in view of the wide dissemination of a nonsuppurative meningoencephalitic process. Case 2 is also a rather unsatisfactory example of circumscribed brain abscess, for these multiple abscesses of the brain were found alongside an extensive sinus thrombosis. Case 8 illustrated how a simple infection of the upper respiratory tract resulted in an abscess of the brain. Should not, however, the complaint of pain over the right eye and the nose and the development shortly thereafter of meningeal signs with marked pleocytosis be regarded as pointing to a rather serious infection of the accessory paranasal sinuses?

In their discussion the authors point to the evolution of brain abscess as consisting of three phases: (1) localized encephalitis; (2) liquefaction and encapsulation, and (3) extension and rupture. These three phases are, of course, descriptive of the rather early and rapidly progressive alterations in circumscribed suppurative encephalitis, but little mention is made of another phase which is exceedingly important and most frequently encountered in cases of abscess of the frontal lobe—the phase of healing. It has been suggested but never proved that brain abscess may undergo spontaneous resolution and healing with scar formation.

In this connection, may I be permitted briefly to report 2 cases in which the process of healing is well illustrated? In 1 case the abscess was fairly well on its way to complete healing, as shown by the histologic preparations. In this case ethmoidectomy with apparent recovery was performed and four months later signs of abscess of the frontal lobe developed. Craniotomy disclosed an abscess, which was drained twice successfully; the third drainage resulted in fatal meningitis. In this case the healing process was permitted to advance for almost five months, resulting in a reduced abscess cavity and a thick wall, well separated from adjacent tissue. Histologic sections through the abscess wall showed it to be composed of dense collagenous fibers.

In another case the frontal and ethmoid sinuses were operated on. There remained a discharging fistula in the right brow, which continued to drain for about eight months. At the end of that period a sequestrum was removed and the fistula closed. Two months later the patient suddenly lost consciousness and generalized convulsions developed. Mental changes and recurrent jacksonian attacks followed. The diagnosis of an abscess of the frontal lobe was made, and the brain was aspirated in various directions, but no abscess was encountered. Postmortem examination revealed a healed abscess in the frontal lobe, represented by a large collagenous scar surrounded by a wide zone of reactive gliosis. Thus, I think, it was established that spontaneous healing of brain abscess does take place and that by repeated drainage the inherent healing potency of the abscess capsule is enhanced.

In 1 of the cases presented a slide was shown in which as many as seven cerebral abscesses were present at various sites. The condition did not look like a contiguous abscess but had all the earmarks of a metastatic process, and there must have been an infection of the blood from which these abscesses originated.

DR. IRA COHEN: I sympathize with Dr. King's view that osteomyelitis is something tangible, something one can bite with a rongeur. To differ a little with Dr. King, in a paper published some fifteen or sixteen years ago, my associates and I reported 4 cases of intracranial abscess following true osteomyelitis of the skull.

There are one or two points of practical interest in connection with this subject. One is that no matter how widespread osteomyelitis may be, involvement of the squama of the temporal bone is rare. The second point is that no matter how small the puffy swelling of Pott may appear on the surface, there is most often a much more extensive area of extradural suppuration than one would be led to believe, and the brain abscess may not be at all contiguous with the site of the small superficial scalp abscess, but centimeters away.

DR. LEWIS D. STEVENSON: May I ask Dr. Globus what caused the death of the patient who had a completely healed abscess?

DR. CHARLES DAVISON: I should like to answer some of the questions. The others will be covered by Dr. Friedman and Dr. Eisenstein.

With regard to Dr. King's question about the differentiation of bone necrosis and osteomyelitis, Dr. Fowler has covered this phase of the problem fully with the excellent slides he presented. How can there be a question of necrosis of bone in these cases in which there was no previous infection?

The second point I want to discuss concerns the fibrosis or encapsulation of brain abscess. In 1 of the cases presented by the authors fibrosis was demonstrated with low magnification, a process analogous to that shown by Dr. Globus with the high power lens. We have not denied the possibility of such an occurrence, but we have mentioned that it is rare. As evidence of this, Dr. Globus was able to collect only 2 cases which he had met in his experience. In our series of about 30 cases of brain abscess of various origins we encountered only 1 such case. I therefore do not believe this to be a common process. This type of fibrosis and healing can be obtained only if the abscess is of long duration.

DR. E. D. FRIEDMAN: As has already been indicated, osteomyelitis may vary in degree and extent, from the puffy tumor to the microscopic lesions which Dr. Fowler has described; all are forms of osteomyelitis. It is a fact that at times microscopic fractures of the skull may lead to subsequent infection of the brain and the formation of an abscess.

It is important to stress the fact that chronic osteomyelitis is more important in producing these complications in the brain than is the acute lesion, just as chronic disease of the middle ear is more apt to cause secondary infection of the brain.

With regard to the encapsulated abscess, there was evidence of healing in one of the slides which Dr. Eisenstein showed, and healing has been described by others. We are not ready to deny that occasionally full healing occurs. There are references in the literature to healed, calcified abscesses, but they are extremely rare.

It has been my feeling for many years that the complications of otitis media (if I may wander off to the subject of abscess of the brain following disease of the ear) are the result of the localized leptomeningitis frequently seen over the tegmen tympani with a lesion of the temporal lobe. There is usually thrombosis of the veins leading from that area, with extension of the process into the brain. If there is venous thrombosis without infection of the clot, one is apt to find the condition which Oppenheim, Adson and Atkinson have described, that is, either localized nonsuppurative encephalitis or hemorrhagic softening. If, however, the clot is infected and the infectious agent travels via this clot into the brain, it produces either an acute abscess or a chronic, low grade infection, depending on the virulence of the organism and the resistance of the host. I believe the same thing is true whether the infection comes from the ear or from a focus in another part of the skull.

Finally, I think the members of the society should voice their gratitude to the gentlemen who have presented their side of the story, and I hope that out of our common counsel the truth will emerge.

DR. JOSEPH H. GLOBUS: Dr. Davison, my material was not so extensive as you seem to imply. The paper which I presented some time ago was based on the study of 16 cases, of which 2 were cases of healed abscess. One out of 8 is a high ratio.

Dr. Stevenson, the patient with a healed abscess died of surgical shock, shortly after aspiration of the brain for abscess during an exploratory craniotomy. There was no meningitis.

DR. JOSEPH E. J. KING: In speaking of osteomyelitis of the skull, surgeons, pathologists and others usually have a definite picture in mind, which should not be confused with that of other diseases affecting the bones of the skull. I feel sure all hold the same general opinion. It may be true that all suppurative conditions involving the bones of the skull are osteomyelitis, but to use the term in connection with such conditions as infection of the paranasal sinuses or the mastoid process is confusing.

Practically all writers, including Mosher, differentiate between disease of the frontal sinus and disease of the frontal sinus complicated by osteomyelitis of the skull. It seems clearer to consider involvement of the posterior plate in disease of the frontal sinus and of the tympanum in disease of the mastoid as necrosis or erosion resulting from infection rather than as true osteomyelitis.

Dr. Cohen has called attention to a fact known to all, that gross osteomyelitis of the cranial vault seldom follows otitic disease, since the lowermost portion of the squama directly connected with the mastoid process contains little or no myelium, while it is not uncommon for gross osteomyelitis of the cranial vault to follow disease of the frontal sinus and ethmoids.

DR. VICTOR W. EISENSTEIN: In answer to Dr. King's practical remarks, I wish to say that the original stimulus for the paper was the fact that there have been some refinements in the diagnosis of osteomyelitis of the skull, by minute foci rather than by the massive lesions, and we are able to explain cryptogenic abscesses in that way. Mosher called attention to the fibrosis in the marrow spaces about foci of osteomyelitis in the skull (Osteomyelitis of the Skull, *Internat. Abstr. Surg.* **69**:417-422, 1939; in *Surg., Gynec. & Obst.,* November 1939).

Electrical Injuries of the Nervous System. DR. LEO ALEXANDER, Durham, N. C. (by invitation).

The injury to vital functions caused by electric shock varies a great deal with the path of the current. A recent investigation (Alexander, L., and Weeks, A. W.: *Am. J. Path.* **17**:601-602 [July] 1941) of cases of electric shock in the Boston area during the past two years has shown that 60 per cent of all fatalities occurred when the current passed from hand to hand and 20 per cent occurred when the current passed from head to foot. The accidents in which current passed from hand to foot, from foot to foot and back to the body caused no fatalities during the past two years, although they constituted 41 per cent of all accidents. It is noteworthy, furthermore, that accidents with a current of 115 volts caused 60 per cent of all fatalities while currents of 2,300 volts and other miscellaneous high tension currents caused only 40 per cent of all fatalities.

An interesting illustration of the importance of the path of current is an accident which occurred recently in the vicinity of Boston. An outdoor transformer had broken down during a storm, and current leaked from the transformer into a rather moist pasture in which three head of cattle were grazing. The pasture was located on a bed of rock and sand, and there was no true ground until about 1 mile (1.6 kilometers) away. The current passed through the pasture, and part of it must have been spanned by the cattle (that is, current passed up and down through the legs and through intervening parts of the trunk), for they were electrocuted by standing on the ground through which the current was passing. A hired man rushed to the scene, and in his case, too, the current passed up one leg, through the pelvic region and down the other leg. However, apart from pain and bewilderment, which made him "jump around considerably," he suffered no ill effects, certainly because his heart and brain were outside the path of the current. In the case of the cattle, however, the current passing through the forelegs must also have passed through the region of the heart. The conditions

of this accident were tested thoroughly by electrical engineering experts, and the farmer was reimbursed by the electric light company which owned the transformer for the loss of his cattle.

In order to understand the pathologic basis for disturbances caused by electric current flowing through the animal or human body in a certain path, Mr. Weeks and I felt that it was necessary to study the distribution of the current throughout the various tissue elements along the path through which the current flows. Ordinary types of measurement seemed of no avail, and in particular the method of investigating the drop in voltage across the path, which has frequently been used in the past, is apt to lead to artificial discrepancies of not quite predictable degree. Therefore we decided to investigate this problem by using a small transformer which could be clamped around any structure within the path of the current without severing that structure or interfering with its conductivity or resistance by application of direct leads. By this method we found that electric current passes through the animal body as though it were passing through a structureless gel, always choosing the shortest path from contact to contact without deflection by anatomic landmarks (Weeks, A. W., and Alexander, L.: *J. Indust. Hyg. & Toxicol.* **21**:517-525 [Dec.] 1939). It was furthermore noted that bone carried amounts of current similar to that carried by all other tissues, presumably because of the vascular bed which pervades living bone as completely as most other tissues of the body. Our study disproved the old fallacy that electric current in the animal body passes along the nerve fibers and the large blood vessels. Our observations reestablish the laws of physics for the living animal body. Physically, the entire animal body is a colloidal system which is in isotonic equilibrium. These colloids are in the sol state in some tissues, such as the blood, and in the gel state in others, such as the most solid tissues. To the electric current the body as a whole, as it is enclosed within the skin, is a uniform mass.

Of particular clinical importance was the observation that when current passed from forefoot to forefoot a significant amount of current passed through the spinal cord. This current was greatest between the fifth and the seventh cervical segment and diminished craniad and caudad. The measurable minimum was reached at the first cervical and second thoracic segments. This observation is of special clinical interest because in lesions of the spinal cord due to accidental electrical injury in man, hand to hand contacts produced most regularly lesions between the fifth and the seventh cervical segment (Alexander, Leo: *J. Indust. Hyg. & Toxicol.* **20**:191-243 [March] 1938; *M. Clin. North America* **22**:663-668 [May] 1938).

In a case of accidental injury of this nature in man the clinical picture of transverse myelitis corresponding to the level of from the fifth to the eighth cervical segment was produced, with sensory loss from the fifth cervical segment downward on the left and from the seventh cervical segment downward on the right, atrophic paralysis of the muscle groups supplied from the fifth to the eighth cervical segment on either side, with clawhand and hand drop deformities, and spastic paraplegia of both legs. In this case current had passed through the head also, and gradually progressive parkinsonian changes (diminution of spontaneous facial expression and prolonged deficiency of mimetic responses) made their appearance one year after the accident, in addition to the transverse myelopathic changes. In the other case a more circumscribed lesion in one anterior horn of the spinal cord, involving the musculature of the fifth to the seventh cervical segment on the left with fibrillations, was the residual.

In order to determine more accurately the amount of current per unit of nerve diameter necessary to produce damage to the nerve tissue, it was decided to study experimentally the sciatic nerve of the cat. The length of time during which irritability and conductivity of the nerve remained disturbed after application of the shock is mathematically correlated to the amperage of the current and the time of its flow. After passage of currents of less than 25 milliamperes per 3 mm. of nerve diameter of five seconds' duration the resultant disturbance is temporary.

A critical level for lasting disturbance, with definite morphologic alterations of nerve tissue, was found to be 30 milliamperes per 3 mm. of nerve diameter for shocks of five seconds' duration. Such shocks produced disability lasting two to three weeks. Morphologically, such nerves show demyelination at the sites through which the current had passed. At these sites the myelin sheaths are transformed into poorly staining, finely granular masses with abolition of Ranvier's rings, Lanterman's incisures and the myeloaxostroma pattern. The axis-cylinders at these sites show swelling and *effilochement* (unraveling). This change is reversible. The animal recovers after two to three weeks, and when it is killed after six weeks the axis-cylinders are on the whole fairly normal except that those in the portion of the nerve through which the current passed have become thinner and finer, as in "healed" plaques of multiple sclerosis in remission. Currents of 25 milliamperes per 3 mm. of nerve diameter of five seconds' duration may occasionally produce paralysis or paresis of four to six days' duration. The morphologic correlate in such cases is a slight degree of swelling of the myelin sheaths and axis-cylinders. Currents of 40 milliamperes and above per 3 mm. of nerve diameter and of five seconds' duration produce irreversible damage to the nerve, with demyelination similar to, but usually more complete than, that produced by currents of 30 milliamperes and with changes in the axis-cylinders consisting of irregular, bizarre, gnarled deformity, transverse fragmentation and longitudinal splitting. This change is not reversible, and if the animal recovers after about four to six weeks histopathologic investigation shows that the portion of the nerve through which the current flowed has been replaced by bundles of young, thin, densely spaced, regenerating axis-cylinders.

These experimental observations are confirmed by an instructive case of an accidental peripheral nerve injury to a youth aged 19. This patient, who had been exposed to an arc from a 33,000 volt circuit, the voltage to ground from which was 19,200 volts, passed current by arc from his left hand essentially to his right foot, the latter having been well grounded; however, some of the current had arced back from the left anticubital space and from the lower part of the abdomen to a grounded transformer case near which he stood. It was calculated that between the fingers and the elbow of the left arm there flowed a current of 38 amperes, between the left elbow and the anterior lower wall of the abdomen a current of 29 amperes and between the anterior lower part of the abdomen and the right foot a current of 24 amperes. Through the nerve trunks of the left forearm, accordingly, there had been flowing a current of 380 milliamperes, or 95 milliamperes per 3 mm. of diameter of nerve; through the nerve trunks of the upper portion of the left arm a current of 290 milliamperes, or 36 to 51 milliamperes per 3 mm. of diameter of nerve and through the right leg a current of 240 milliamperes, or 30 to 34 milliamperes per 3 mm. of diameter of nerve. After the injury the left arm was paralyzed and desensitized and the right leg paretic. Corresponding fairly closely to our prediction based on our experimental work, the right leg recovered on the tenth day after the injury, the left upper arm began to improve during the third week after the injury, while from the elbow down the forearm and hand remained paralyzed and desensitized for about one year. This was probably due to the fact that the nerves of the forearm and hand failed to regenerate readily, because of scarring in the antecubital fossa and between the partly charred muscles of the forearm. During the second year after the injury, however, a great deal of regeneration took place even here. One and a half years after the accident this regeneration had progressed to restitution of sensation in the distribution of the ulnar nerve down to the tips of the three fingers supplied by that nerve and to restoration of significant activity in the thenar and hypothenar muscles.

Summary.—A clinicopathologic and experimental study of electric shock is presented. Experimental study shows that electric current passes through the animal body as though it were passing through a structureless gel, always choosing the shortest path from contact to contact without deflection by anatomic landmarks.

Living bone carries a similar amount of current, presumably because of the vascular bed, which pervades living bone as completely as most other tissues of the animal body. A critical level for lasting disturbance, with definite morphologic alterations of nerve tissue, was found to be at 30 milliamperes per 3 mm. of nerve diameter for shocks of five seconds' duration. Lower values produce temporary disturbance, the duration of which is mathematically correlated to amperage and time. These experimental observations are applied to the interpretation of the clinicopathologic findings in cases of accidental injury in man.

DISCUSSION

DR. LEWIS D. STEVENSON: In the cases of legal electrocution in which I have had opportunity to make examinations—perhaps a dozen or more—cases which Dr. José Nonidez, of Cornell, has studied carefully by various methods, the changes were surprisingly slight. In these cases we did not observe any of the splitting or fissuring of the brain that has been described by Hassin. We did not find much damage to the larger arteries, with the splitting of the internal elastic membrane that Hassin has observed. I think we did not note the alterations in the oligodendroglia or the reactive changes in the glia which he has described, but we did see a few axonal and other changes in the neuron. Immediately under the electrodes one could see a number of swollen cells with the Nissl granules somewhat displaced, and by means of the Cajal reduced silver method and the Bielschowsky method we noted fragmentation of the neurofibrils in a few cells. Also, we observed apparent displacement of the pigment to the periphery of the cell body; sometimes it seemed to be almost outside the cell. By Golgi's method, by which a complete silhouette of the nerve cell body and its fiber can be obtained, no change whatever could be demonstrated. There was no fragmentation of the axon as a whole.

The brains in cases of legal electrocution seem to be somewhat coagulated by the heat—I suppose because there is great heat within the skull and in the spinal canal. They do not flatten out on the table as does the ordinary brain. But such brains also showed a surprising absence of hemorrhages, even with a current of 2,000 volts and over. Dr. Alexander, in one of his other papers, showed a few small hemorrhages and some loss of myelin in the white matter of the brain.

Except for the changes described, we thought the most conspicuous change in the brain in cases of legal electrocution was shrinkage of the small vessels away from the brain substance. There is quite a space around the small vessels in the cortex. This is a result of the contraction of the muscles in the vessel wall, a condition which is prominent in the aorta of electrocuted persons.

I should like to ask Dr. Alexander whether he has seen any cases in which the current was accidentally transmitted across the cord, and, if so, what the pathologic picture was.

DR. ARMANDO FERRARO: The conclusion reached by Alexander and Weeks from use of the clamp transformer that the electric current passes through the animal body as though it were passing through a structureless gel, always choosing the shortest path from contact to contact without deflection by anatomic landmarks, is, in my opinion, a definite progress in electrophysiopathology.

I am particularly interested in the electrical damage of the brain because of the recently introduced electric shock therapy advocated by Cerletti and Bini, a method which is being applied in the United States on an ever increasing scale for the treatment of so-called functional psychoses. In the literature one finds scanty data on pathologic changes following the passing of light currents of short duration through the brain, as is the case in electric shock therapy. From a personal conversation which I held with Bini, one of the authors of the electric shock therapy, it seems that following the application of current for that purpose, which, as is well known, is one of 100 to 120 volts, 200 or 300 milliamperes' intensity and one-tenth or one-fifteenth second's duration, the histopathologic changes

in the brain tissue are of a reversible type and involve chiefly the nerve cells, which may undergo acute swelling or chromatolysis. With the cessation of the current the morphologic pattern presumably returns to normal.

In contrast to these reports, I have received preliminary information concerning changes on which Dr. Bernard Alpers will report at the next meeting of the American Association of Neuropathologists, when experimental electric convulsive therapy will be under discussion. In the brains of 4 animals already examined in a series of 17, study of which is in progress, hemorrhages were present in the subarachnoid spaces, resulting in fibrosis of the pia-arachnoid in 2 instances. Most significant is the occurrence of hemorrhages within the brain substance. In 2 cases large hemorrhagic infarcts, and in another numerous punctate hemorrhages in the cortex and white matter, were noted.

It is my opinion that, as far as man is concerned, no serious after-effects attributable to damage to the brain have resulted from thousands of applications of the electric current and that one may feel safe in continuing to apply, within the intensity and duration advocated by Cerlutti and Bini, electric shock therapy to patients with mental disease.

The mechanism of death following passage of very intense electric current through the human body is another important question raised by Dr. Alexander. There must undoubtedly be a difference whether current passes through the heart or through the brain alone or through both. I feel that in certain cases cardiac and respiratory failure may be of peripheral reflex nature, but that in other cases acute cerebral damage, mostly of a functional vasomotor type (stasis and prestasis or vasoconstriction and vasodilatation), affecting the central regulation of respiration and circulation is responsible for what might be called cerebral death.

Dr. Donald Shaskan: At the laboratory of experimental neurology at New York University, my associates and I have also found that there is some tendency for small electric currents to produce damage to the brain. We do not know whether this change is reversible or irreversible. We do know that the oxygen metabolism is interfered with (Wortis, S. B.; Shaskan, D.; Impastato, D., and Almansi, R.: Brain Metabolism: VIII. The Effects of Electric Shock and Some Newer Drugs, *Am. J. Psychiat.*, to be published); I should like to ask Dr. Alexander to state again the duration of the current. As Dr. Ferraro has stated, the current most often used in electric shock therapy runs for one-tenth second.

Dr. Charles Davison: I should like to ask whether Dr. Alexander found any pathologic changes in the basal ganglia in the cases in which parkinsonian symptoms appeared. I am asking this question because in a previous case which I studied histopathologically the electric current passed through the optic nerve and caused bilateral necrosis of the basal ganglia.

Dr. Leo Alexander: First, in answer to Dr. Stevenson: I should have stressed more strongly that there are different types of electric damage to the nervous system: the direct neuronal damage caused by the electric current itself and the indirect neuronal damage secondary to circulatory disturbances caused by the current; furthermore, there is frequently the complicating factor of heat. We have selected for this presentation the type of damage which we considered to be direct and primary, and in our experimental work we have eliminated the factor of heat.

We began this work before electric shock therapy came into vogue. We started with electrical accidents, but we tried to investigate some of their basic biologic aspects.

After legal electrocution, with passage of current through the head, there are almost complete coagulation and hardening of the brain, as in "fixation of tissue by heat." Legal electrocution is an extremely efficient method of interrupting vital processes suddenly and completely; therefore structural changes of the brain beyond the general rapid coagulation do not have time to develop. I am sure Dr. Stevenson will agree that in the present practice of legal electrocution the interval from passage of current to death is extremely short. I am interested to hear

that he found, however, some fragmentation of neurofibrillae, for that is what we observed in the peripheral nerves in our experiments; this is probably a primary electrical effect.

The cases in which I described hemorrhages and perivascular necrosis, degenerations and demyelinations were instances of accidental electrocution in which the current passed through the heart. They illustrate indirect, circulatory damage to the nervous system. Frequently, as Jellinek has shown, the patient does not die immediately, but many hours later, and the pathologic changes in the nervous system developed gradually as the result of circulatory disturbances. I agree with Jellinek and with Maclachlan in the opinion that in many of the cases of accidental electrocution in which the current passes through the heart the patient does not actually die until six to twelve hours after the shock; i. e., he passes through a period of suspended animation or "apparent death." Maclachlan revived a patient after eight hours of what appeared to be death according to most of the usual criteria, except for the absence of rigor mortis and livid patches. In the course of an experimental study, Drs. Maxwell E. MacDonald, Tracy J. Putnam and myself obtained records on cats so electrocuted (i. e., through the region of the heart) in which no pulse could be detected by palpation and respiratory activity was absent; however, blood pressure tracings of the femoral artery showed that a fine trickle of circulating blood, with irregular and widely spaced, feeble pulse, persisted. Prior to this long period of throttled-down circulatory activity there was a brief period (one to three minutes) of complete circulatory standstill. Such cats could be fully revived by artificial respiration continued for several hours. The same is true in cases of injury by lightning.

Most of the cases in my experience in which lasting cerebrospinal disturbances developed later were those in which current passed through parts of the central nervous system; i. e., in most of them the damage to the nervous system was primary. In some of our cases in which parkinsonian symptoms appeared, the circulatory disturbance was primary and the damage to the nervous system secondary. In 1 of my cases of electrical injury in which the current passed through the region of the heart I found focal areas of necrosis in the anterodorsomedial portion of the globus pallidus, i. e., in the region which is first and most regularly affected in carbon monoxide poisoning. A lesion of the same type has also been described by Dr. Ferraro in cases of cyanide poisoning and by Dr. Courville in cases of nitrogen monoxide poisoning. All these lesions are essentially due to circulatory disturbance.

DR. ARMANDO FERRARO: How did the current pass?

DR. LEO ALEXANDER: From an area measuring 5 cm. in diameter on the right side of the back between the dorsal portion of the spine and the inferior angle of the right scapula to an area extending 10 cm. to the left from the lower lumbar and sacral portions of the spine, that is, presumably through the heart. I think the cerebral damage in this case was due to the prolonged circulatory disturbance.

DR. ARMANDO FERRARO: In the laboratory of neuropathology of the Psychiatric Institute we have at present the brain of a person in whom a parkinsonian syndrome developed after the passage of a high voltage current from hand to hand. The brain is presently to be studied.

DR. LEO ALEXANDER: In hand to hand contacts cerebral changes are not due directly to the current but are caused by the prolonged circulatory disturbance produced by passage of the current through the heart and the endings of the vagus nerve. It is interesting that in the majority of the cases in which deep shock existed for many hours no lasting cerebral symptoms or lesions developed, presumably because in deep shock the oxygen requirement of the tissues is greatly reduced and can well be met by the faint trickle of circulating blood which we have found to persist in spite of pulselessness as observed by the usual methods of clinical examination. It is likewise known that in a great number of cases of carbon monoxide poisoning cerebral changes do not develop. This fact is

encouraging to those engaged in perfecting methods of resuscitation; in the vast majority of instances lives of citizens will be saved who will remain active, useful and healthy. The fact that lasting electrical injuries occur occasionally has been misused to encourage defeatism in endeavors at resuscitation.

Dr. Stevenson asked about the histopathologic nature of the injury to the spinal cord produced by electric current. Unfortunately, I do not have a case of accidental injury in man with necropsy. A case was described by Linck (*Beitr. z. path. Anat. u. z. allg. Path.* **102**:119-142, 1939) in which degenerative changes were present in the gray and the white matter of the cord, but the author presented only Weigert sections, which did not allow conclusions as to the more elementary and fundamental histopathologic nature of the disease process produced. Unfortunately, the man with injury to the spinal cord whose neurologic status I demonstrated to you by motion picture died, but permission for autopsy was not obtained.

Dr. Ferraro mentioned hemorrhage. I have seen perivascular and small parenchymatous hemorrhages in cases of accidental injury in man in which the electric current passed through the heart region from contacts located on the body or on the body and one extremity. Similar hemorrhages were observed by us in experimental animals with foreleg to crossed hindleg and with foreleg to foreleg contacts. Hemorrhages were also seen in experiments in which current passed through the vasomotor center of the medulla oblongata, but I am not prepared to state whether they occur regularly in experiments in which current passed through the cerebral hemispheres only, comparable to the arrangement prevailing in therapeutic electric shock in man. In our present quantitative study of the pathogenic effect of known amounts of current flowing for known periods, we have so far limited ourselves to peripheral nerves, because in these nerves irritability and conductivity and their thresholds can be tested accurately and the exact quantitative data obtained thereby for nerves of known diameter can be expressed in clearcut fashion by curves. The brain is less accessible to quantitative study. However, we have seen vasomotor phenomena occurring with significant regularity in all peripheral nerves which were shocked with a current of sufficient magnitude to abolish irritability and conductivity temporarily, even if only for part of a minute. Immediately after the shock, when irritability and conductivity of that part of the nerve through which electric current had flowed are abolished, that portion of the nerve appears blanched and its blood vessels become constricted and anemic; shortly before conductivity and irritability return, this part of the nerve blushes and its blood vessels become engorged. Finally, some time after the return of conductivity and irritability, the nerve resumes its former normal appearance. The duration of this vascular disturbance (blanching followed by congestion), like the neuronal disturbance of irritability and conductivity, is proportional to the amperage of the current and to the duration of its flow. The period of blanching is always terminated before and the period of congestion after the reappearance of irritability and conductivity. Occasionally in cats killed shortly after the shock small perivascular hemorrhages are seen in the parts of nerves through which current had been flowing. These small perivascular extravasations in the peripheral nerves, however, are probably insignificant and are readily and easily absorbed, for they are absent in the vast majority of animals killed several days to weeks after the shock. In only 1 animal, which was killed three days after passage of a current of 40 milliamperes for five seconds through the right sciatic nerve had paralyzed that nerve, did autopsy show extensive hemorrhagic extravasations throughout the part of the nerve through which current had been flowing; this area was sharply demarcated from the adjacent normal portions of the nerve which had not been directly exposed to the current. This hemorrhagic extravasation must have taken place some time after the shock, for it was not present immediately after the shock, up to the time of surgical closure of the wound. There is, in addition, a late and lasting vascular change, consisting of hyaline degeneration of vessel walls, which manifests itself

weeks or months after the electrical injury and occurs with significant regularity in nerves and other tissue through which electric current in excess of 25 milliamperes per 3 mm. of diameter has passed for five seconds. This late hyaline change in the arteries and veins is similar to that which occurs after excessive roentgen irradiation. These observations raise the question of cerebral lesions incidental to electric shock treatment, which Dr. Ferraro mentioned, in relation to their significance both as a factor in the clinical improvement produced and as a possible contraindication to such treatment. I have no opinion in this matter as yet. The answer is left to those who investigate the nature and efficacy of such treatment; I plan to take part in a clinicopathologic and experimental study of this problem in the near future.

The pathogenic effect of electric shock is proportional to the amperage and to the duration of flow of electric current. The amperage is more important than the duration of flow; that is, the increase in pathogenic effect produced by an increase in amperage of the current is greater than that produced by a similar increase in the time of flow of the current.

Dr. Shaskan's question is an interesting one. I have heard of a man who became aphasic after a shock similar to that used in electric shock treatment and remained so for two weeks, and of another who had disturbance of memory of similar duration. In these instances temporary cerebral disturbance was probably due to reversible changes of a nature consistent with swelling of axons and ganglion cells. The figures for our experimental results, which I gave in detail, are those based on five second shocks, which constitute by far the largest number in our series. The injured boy whose picture I showed last was exposed to the electric current for two seconds, and still the figures for the recovery periods of those peripheral nerves which were restored corresponded fairly well to our experimental results with comparable currents of five seconds' duration. There appears not to be much difference in pathogenic action between two second and five second shocks. There is more difference in pathogenic action between five second and ten second shocks. There is, of course, a great deal of difference in pathogenic action between shocks which last only a fraction of a second and those which last one or more minutes.

PHILADELPHIA NEUROLOGICAL SOCIETY

JOSEPH C. YASKIN, M.D., *Presiding*

Regular Meeting, May 23, 1941

Intracranial Pneumocele: Report of a Case. DR. H. WYCIS.

Roentgenograms of the head taken the day the bullet wound was sustained were shown.

Pathologic Study of a Monkey Exhibiting a Behavior Disorder. DR. FREDERIC H. LEAVITT and DR. HELENA E. RIGGS.

The monkey whose picture is seen in the film and specimens of whose brain Dr. Riggs will show in the slides was a resident at the Veterinary Hospital of the University of Pennsylvania for about a year, where his behavior was observed by several classes of veterinary students and by a number of medical men.

The history, in brief, is that at the time this monkey was killed he was about 3½ years of age, which would place him in the "adult" class of simian growth. When about 2½ years of age he was brought to the veterinary school by his master, a policeman on the city force, who said that about the time the monkey attained growth maturity he had begun to exhibit behavior which made him an

undesirable resident in his home. There was no history that the monkey had ever been asphyxiated or had had any disease or been in any situation which would have deprived him of the average normal amount of oxygen. We mention this with reference to the pathologic changes. At about the time he gained maturity he changed from a sociable monkey, who had liked companionship, to one of asocial characteristics. He became seclusive and remained by himself. He would not respond to the usual approaches and petting of his master. He then acquired the obnoxious habit of sucking his own penis, which act he performed constantly. This malignant behavior became such that it was impossible to keep him in the home, and he was sent to the University of Pennsylvania Department of Veterinary Medicine, where he remained about a year. Soon after his arrival there he was castrated, in the hope that this would break him of his vicious habit, but the operation did not achieve its purpose. He would sit in his cage in a corner, apparently entirely oblivious to what was going on around him, and then suddenly bounce up and down, and with his arms tear at his hair or at his face, viciously bite himself on his forearms and his legs and throw himself against the side of his cage. On other occasions he would roll over on his back on the floor and behave as though he were very angry at something.

One of us (Dr. Leavitt), with others from the psychopathic department of the Philadelphia General Hospital, observed the animal and reported to the veterinary department that in his opinion not much could be done for the monkey, as he was not a fit subject for shock therapy. The animal was therefore killed. Dr. Riggs did a complete postmortem examination immediately after the animal was killed, thus giving little chance for postmortem change in the brain.

The essential psychologic picture presented by this monkey was that of a change of personality occurring at the time of adolescence, partaking of the nature of an introvertive behavior pattern and the affective state comparable to that of a schizoid psychosis in man.

Neuropathologic Study.—The animal was a young adult rhesus monkey; apart from the behavior disorder he was in good health. He was killed by pentobarbital sodium anesthesia, with a minimal agonal period, and a prompt and thorough necropsy revealed no organic visceral disease which might have complicated the lesions in the brain.

Grossly, the brain appeared normal. Microscopically, there was evidence of chronic stagnation of cerebral blood flow, increased capillary permeability and secondary diffuse degeneration of nerve cells and myelin. The cellular degeneration was not uniform but appeared most intense in the deep layers of the cortex, the pallidum, the Purkinje layer and the vegetative centers of the hypothalamus and brain stem. Even in the deep cortical layers the degeneration was not uniform but was greater in the association areas than in the projection centers. This was particularly noticeable in the occipital lobe. The visual projection cortex showed minimal involvement, while in the adjacent association areas the second, third and fourth layers were almost completely wiped out.

The changes in the brain of this monkey with a behavior disorder are comparable to those described by Chornyak as produced by anoxia. They are also comparable to the changes we have found in the brains of young persons dying during an acute psychosis uncomplicated by systemic disease. Admittedly, the pathologic changes are not diagnostic of a behavior disorder, but it is doubtful whether in any disorder the clinical symptoms can be closely correlated with specific pathologic alterations in the nervous system. In many cases of encephalitis the brain shows no evidence of inflammatory reaction; the clinical picture produced by a leaking cerebral aneurysm may in no way differ from that caused by acute purulent meningitis. In less than 50 per cent of cases of dementia paralytica at the Philadelphia General Hospital the brain shows the supposedly specific pathologic picture even when the clinical diagnosis is corroborated by the serologic reaction of the spinal fluid and the colloidal gold test. Indeed, in view of the elasticity of diagnostic criteria and the protean manifestations of behavior disorders, it is difficult to conceive of any specific alterations in the nervous system which would cover all aspects of such conditions.

Although pathologic alterations due to anoxia may occur in the nervous system in many conditions in which behavior disorders play only a minor role, the fact that organic changes in the brain are present in cases of the so-called functional psychosis is too important to be disregarded. In view of the experimental and clinical evidence of association of psychic dysfunction with oxygen deficiency, a physiologic interpretation of nonspecific organic changes in the brain accompanying behavior disorders may provide a dynamic approach to the problem of psychic dysfunction.

Conclusion.—The organic pathologic changes in the cerebral cell layers of this animal are comparable to those found in the organic psychoses. The clinical history of the monkey is similar to that noted in man in an introvertive schizoid psychosis. This clinicopathologic study is offered as a contribution to the micropathology of abnormal behavior patterns in a simian vertebrate.

DISCUSSION

DR. MICHAEL SCOTT: I am wondering whether the changes in this case might not be related to vitamin deficiency and whether, in view of the question of masturbation, there was any sign of irritation of the cells of the spinal cord.

DR. J. C. YASKIN: This is an interesting case of schizophrenia in a monkey. Dr. Riggs, were there any changes in the pituitary body? When was the monkey castrated—how soon before he was killed?

DR. FREDERIC H. LEAVITT: The monkey was castrated about one year before he was killed. His abnormal behavior began about eighteen months prior to castration, which was coincident with puberty. The history is of interest in that there was a similarity between the behavior of this monkey and that of a great many psychotic adolescents whom we see at the Philadelphia General Hospital. He exhibited change of personality, became seclusive and antagonistic and behaved in a manner which was at variance with the training he had had. That was a situation which was, as Dr. Yaskin stated, schizophrenic in its nature. There is no history of avitaminosis. As far as the veterinary department could determine, his food had been adequate, and while at the hospital he was given a well balanced monkey diet.

DR. HELENA E. RIGGS: The contribution of neuropathology to the study of behavior disorders has necessarily been meager. Such disorders per se are not usually fatal, and in chronic forms the relation of changes in the brain to the mental state is obscured by the complicating factor of associated physical deterioration. Even in the rare cases in which a young person dies during a period of acute psychosis the interpretation of the pathologic changes in the brain is open to question. Because of the acute clinical course and the fatal outcome, both the behavior disorder and the changes in the brain may not be characteristic of the typical functional psychosis. In the case Dr. Leavitt and I are presenting we believe we are justified in interpreting the cerebral lesions as a causal factor in the behavior disorder.

I think Dr. Leavitt answered Dr. Scott's question in saying that the changes were nonspecific. When the monkey was observed in the veterinary school, the question of the possibility of an avitaminosis at some period of his life was considered. The neuropathologic changes were no more extensive than those I have observed in brains of patients with psychoses. We did not save the spinal cord. The pituitary gland was not involved; there were not the number of castration cells one would expect. Experimental workers have found in lower animals that irritative changes in the hypothalamus may produce behavior disorders.

Pitressin-Inhibiting Substance in the Serum of a Patient with Transient Diabetes Insipidus. DR. R. B. RUTHERFORD and J. Q. GRIFFITH.

A 35 year old woman had suffered for many years from attacks of diabetes insipidus, of several months' duration, interspersed with periods of remission. She was studied during an attack and later during a remission. During the attack it

was found that her serum inhibited the antidiuretic action of pitressin for rats. During the remission the serum itself contained an antidiuretic substance, as tested on rats. Definite conclusions could not be drawn, but the effect of an unstable balance between the anterior and the posterior lobe of the pituitary is suggested.

DISCUSSION

DR. GEORGE GAMMON: One is usually forced to depend on some secondary result rather than check directly on the presence of the hormone in the circulating blood. Therefore the test the authors have developed is of definite value. I should like to ask Dr. Griffith what this test shows when one removes parts of the pituitary, the anterior or the posterior lobe.

DR. J. E. WEBSTER: I should like to ask what experience Dr. Griffith has had with respect to the relation of headache to the antidiuretic hormone and whether or not headache of unknown origin may be associated with water retention.

DR. J. C. YASKIN: In my experience, diabetes insipidus is uncommon, and the diagnosis in most suspected cases turns out to be that of brain tumor. Thus, one should be mindful of the possibility of tumor, encephalitis or structural disease with irreversible changes.

DR. J. Q. GRIFFITH: In reply to Dr. Gammon's question: To control this test by removing parts of the pituitary, one would have to find a way of producing a hyperpituitary subject. We think we have such an experimental animal, but we have been able to produce such a condition only during the last two or three weeks, after considerable work. The work is in progress but has not been completed. Some patients had a positive antidiuretic action of the serum, which can be made negative in 80 to 85 per cent by irradiation of the pituitary. The reaction of the serum then remains negative, perhaps definitely or perhaps only for five months. We have had recurrence of a positive reaction in five months.

As to the headaches, we have had a series of patients, 7 or 8 of them, who have had irradiation of the pituitary and who show antidiuretic substances in the blood. Some have had headache without hypertension. Some have had dramatic relief of headaches without the antidiuretic action being changed from positive to negative. I do not know much about diabetes insipidus; the patient may well have had a pituitary tumor, perhaps for fifteen years. Certainly, our observations have been more or less incidental to a larger problem.

Response of Human Brain Tissue to Local Refrigeration. DR. TEMPLE FAY.

Five cases in which a metal capsule had been inserted into the brain to a depth of 3 to 9 cm. were presented. The capsules were hollow and permitted the flow of refrigerated solution, so as to reduce the temperature of the tissue surrounding the capsule to various levels. A temperature of 40 F. was chosen because I had observed that this level of temperature inhibited tumor growth and did not destroy skin and other tissue cells.

The capsules were retained in place as long as two hundred and ten days, specimens for biopsy being taken frequently from the tract and autopsy material analyzed for the effect of this temperature on adjacent tumor and normal brain tissue.

Four cases of glioblastoma and 1 of astrocytoma were studied. Neuropathologic examinations by Dr. L. W. Smith and Dr. M. Sano indicated regressive changes secondary to the influence of cold applied over long periods.

In the case of astrocytoma a temperature of 20 F. was maintained in the region of the capsule for more than one month; the capsule, which extended close to the thalamic area on the right, did not affect the function of the left hemisphere, as the patient was right handed, and speech, understanding, memory and vision were retained in the normal hemisphere, although the deep tissue temperatures adjacent to the capsule were 80 F. below normal (20 F.).

These observations indicate that normal human brain tissue can withstand a temperature of 20 F. for prolonged periods and that certain regressive changes occur in tumor tissue exposed to 40 F. for prolonged periods. (The film was then shown.)

DISCUSSION

DR. F. C. GRANT: How about the effect of the capsule itself, aside from that of cold? Dr. Fay showed certain reactions in the brain that he held were due to cold; yet I wonder how much was due to cold and how much to the presence of the capsule, without change of temperature?

DR. TEMPLE FAY: In this work my colleagues and I attempt to maintain an even temperature about the capsule. If we set the capsule at 40 F., the temperature of the machine which delivers the fluid must be lower than 40 F., because the brain heats the fluid. We have taken not only the temperature of the tissue adjacent to the capsule during the time the machine was running, to check on the machine, but also the temperature during the replacement of the capsule and the temperature around a thermocouple and have found that it was remarkably reduced. In 1 instance, in which the capsule was present in one of the ventricles, the cerebrospinal fluid taken from the other ventricle was 94 F.; so the whole brain must come into the picture to some extent, although the other hemisphere probably does not participate in the changes.

I shall mention one experience because it may lead further. In 1 case, when we lowered the temperature to about 28 F., the man would go to sleep; however, he was quite willing to wake up when the temperature was 38 F. In this case the capsule was placed on the left. The temperature was just low enough to make him drowsy and sleepy. This did not occur when the capsule was placed on the right side.

In these cases the capsule tracts showed no reaction, but there was a slight reaction around the surface of the wound. If we left the capsule in we did not get an infection. In the first case, we had to replace the capsule twice, because every time we took it out the infection would flare up. We have now used this method in treatment of brain abscess, and I have a very small series in which the capsule was placed in the abscess itself. We are hoping with the aid of drugs to promote healing in cases of this condition.

DR. ERNEST A. SPIEGEL: The physiologic side of the question is interesting. Some years ago Trendelenburg made similar tests on monkeys, in which he placed capsules over the motor area, and the monkeys continued to walk around happily and unconcerned. He turned on the apparatus and lowered the temperature, and paralysis developed. When he raised the temperature again paralysis disappeared. Some similar experiments had been made by Bárány on the human cerebellum. In trying to localize the centers he studied a number of cases in which he had operated for cerebellar abscess or tumor. In these cases he simply froze the skin, in the hope of lowering the temperature of the underlying cerebellum. How far the effect extended is difficult to say, but I believe he could localize certain centers. A similar type of experiment with the cortex has been made by applying different degrees of temperature to various parts of the occipital lobe. It is interesting to see the effect of these changes of temperature on the basal ganglia. In my laboratory, an apparatus like a small cannula was devised. It was introduced into the corpus striatum, and a puncture was made. After such a puncture the animal manifested fever. When hot water was introduced into the capsule, the temperature was reduced. When cold water was introduced, the fever recurred. It was concluded that the cold water had a stimulating action on the mechanism for temperature regulation, while an increase of temperature had the opposite effect.

Experiments were carried out on the carotid arteries of dogs. Water at different temperatures flowed throughout the cannula, first warming and then cooling the temperature of the blood in the carotid arteries. In this way my associates and I were able to study the effect of change of temperature of blood in the brain on the body temperature as a whole, with similar results. The question, of course,

arises as to just how far such experiments on a relatively normal brain are comparable to experiments on the pathologic brain, in which the tumor has developed for a certain time and has infiltrated the neighboring brain tissue and already changed its function. It is quite feasible, therefore, to conclude that a different result may be obtained in a brain in which a tumor has existed for a considerable length of time and compensatory mechanisms have already been established.

DR. MICHAEL SCOTT: Some of the symptoms seem to be endocrine in nature. Dr. Fay mentioned the question of sleep. On one occasion I saw a patient exhibit a marked increase of appetite; he ate a huge amount of food and was hungry at all times. We also checked for changes in dextrose tolerance and carried out basal metabolic studies. In 3 cases bulimia was the outstanding symptom.

DR. TEMPLE FAY: I should like to answer Dr. Spiegel's point by saying that most of these experimental observations have been fairly brief. I do not know how to evaluate the result from the clinical point of view. Our recordings go on for days, most of them without revealing the hyperthermia that one hears about. I am inclined to feel that too much value is given to physiologic explanations of how animals react, as compared with how human beings react. I know that these patients have been subjected to temperatures below the normal level of 100 F. that is usually found in the brain. At 90 F. they should have a chill. We have known the entire hemisphere to be as low as 95 F. within 5 cm. of the capsule. Dr. Wycis observed terminal hyperthermia in a patient who was in an unconscious post-traumatic state. The patient's temperature was 106 F., and the pulse was correspondingly high. We decided to reduce the temperature by means of refrigeration. The temperature slid on down to 92 F. before we could check the refrigeration. The interesting thing was that the patient became conscious. With his temperature at 90 F. he stayed conscious for three days. In a second case, the patient seemed about to die on the second day with the same clinical picture. After we lowered her temperature to 90 F. the pulse and respiratory rates and the temperature fell and normal metabolic function eventually returned.

We had another case of trauma which was interesting. We have concluded that when trauma is associated with shock and subnormal temperature, the subnormal temperature may be a beneficial defense mechanism that should be encouraged. Allen, of New York, treats patients with distal circulatory disturbance by holding the leg at a low temperature, and in that way he can conserve the leg from gangrene. When he brings the temperature back to normal he says that gangrene sets in. Circulation is probably sufficiently delayed for the preservation of tissue. The intestine has been ligated and kept at 40 F. without becoming gangrenous, but has become gangrenous at normal temperature. A metabolic change, with low oxygen need at a lower temperature, may be partly responsible.

Much must be learned about the physiology of the body at a temperature of 90 F., then 85 F. and then perhaps 70 F. before any conclusions can be drawn about what may happen in these cases.

Prevention of Traumatic Complications in Convulsive Shock Therapy by Magnesium Sulfate. DR. H. EDUARD YASKIN.

This paper was published in the July issue of the ARCHIVES, page 81.

DISCUSSION

DR. TEMPLE FAY: I think Dr. Yaskin deserves much credit not only for introducing a new idea (new in its application) but for making possible a greater variety of studies than would be permitted by the use of one drug only in the control of seizures. Back in 1921, when magnesium sulfate was a popular oral preparation for production of dehydration in cases of injuries to the head, Gwathmey came from Boston to ask me how much central effect I thought the magnesium sulfate had in controlling convulsive seizures. At that time I could

not see any particular central effect, and I did not believe that it had any. Subsequently, in looking up the literature, I found he suggested that the drug be used intravenously. He was using it as a fortifying agent in induction of anesthesia. I found an article by an English surgeon in India, published in 1911 or 1912, who reported that ulcerative colitis, and other complications, resulted from the introduction of magnesium sulfate intravenously. That made me afraid to use it clinically. Later, however, magnesium sulfate was employed intravenously by workers in one of the state hospitals in Ohio as a sedative to quiet one of the inmates. They wrote to me, and I warned them about this form of administration. I have not seen the English surgeon's early warning verified or repeated.

DR. GEORGE GAMMON: I should like to ask Dr. Yaskin several questions. What accounts for the short duration of the paralysis? Do all such curarizing agents act so short a time? It is true of quinine compounds and of curare derivatives given in smaller doses. I was surprised, Dr. Yaskin, that you could get such complete weakness and relaxation and that it would then wear off so rapidly. Have you any idea of the level to which you raise the magnesium sulfate of the blood by this treatment?

DR. H. E. YASKIN: I want to thank Dr. Fay for his remarks. As to Dr. Gammon's questions: I cannot yet explain the short duration of the action. Apparently, the concentration of magnesium sulfate in the serum is not high enough to have any lasting value. I have not observed clinically any respiratory or cardiac complications. Two authors have reported heat-producing sensations when the drug was used as a circulatory agent. They used it to determine circulation time, and they employed it in cases of pregnancy with marked cardiac disease. They were not able to discern any particular abnormalities. However, it must be remembered that they used a concentration that was less than mine—10 per cent, instead of 25 per cent. As regards its use in metrazol and electric shock treatments, I think it has the disadvantage of any preparation which has to be given intravenously; that is, it is a fairly potent solution, and one must be careful that it does not get outside the vein in order to prevent phlebitis and sclerosis. Again, many patients complain of the sensation of heat they experience prior to the metrazol shock treatment. They resent that very much.

Vertical Nystagmus Associated with Cerebellar Lesions. DR. ERNEST A. SPIEGEL and DR. N. P. SCALA.

Experiments on cats showed that a cerebellar type of vertical nystagmus exists other than that produced by lesions of the vestibular nuclei. This cerebellar form of vertical nystagmus was observed after lesions of the vermis with the vestibular nuclei and their fiber systems histologically intact. The intensity and, to a certain degree, the direction of this nystagmus are influenced by the position of the head. The change from the normal to the abnormal position may not only increase the frequency and amplitude of the nystagmus but also influence its direction. When in the normal position an animal with a lesion of the vermis usually shows a downward deviation of the eyeballs and/or a preponderantly vertical nystagmus of low frequency, with the fast component toward the upper or the lower lid.

After the animal has been brought to the supine position there usually appears a nystagmus toward the lower lid, of higher frequency and sometimes also of larger amplitude than when the animal is in the normal position. Thus, the nystagmus toward the upper lid which appears when the animal is in the normal position may be reversed in its relation to the orbit. Combination with deviation of the eyeballs, toward the lower lid chiefly, and/or with a rotary component of the nystagmus in one or both eyes could be observed in the normal as well as in the supine position. With the animal in the lateral position the nystagmus usually beats parallel to the palpebral fissure or somewhat obliquely, with the fast component toward the upper ear, or rotary nystagmus is observed, usually when the animal is in the left or the right lateral position.

The frequency, and often also the amplitude, of the nystagmus diminish rather rapidly after the animal has been placed in the abnormal position.

It seems particularly noteworthy that in a number of cases nystagmus appeared only when the animal (head) was in an abnormal position. This could be observed particularly when small lesions had been placed.

Neck reflexes were avoided by keeping the head and body of the animal in a fixed relative position on the board. In a number of experiments retinal impulses were eliminated by covering the anesthetized corneas with a small rubber membrane that was blackened with india ink. This had no effect on the positional nystagmus. Finally, bilateral labyrinthectomy was performed on animals which showed typical positional nystagmus after ablation of the lobus medianus posterior. After elimination of the labyrinths a weak spontaneous vertical nystagmus (a few jerks per minute) could still be observed, but change of position of the animal no longer influenced the amplitude or frequency of this nystagmus.

The positional nystagmus observed after a paleocerebellar lesion probably belongs in the group of symptoms of overexcitability of the vestibulo-ocular reflex arc that follow such a cerebellar lesion. One may perhaps assume that in this state of overexcitability there occurs not only an increase of discharges from the vestibular nuclei to the eye muscles, resulting in "spontaneous" nystagmus, but also a spread of impulses originating in the static receptors of the labyrinth to those parts of the vestibular nuclei which transmit kinetic reactions to the eye muscles. Owing to such a spread, impulses from the static receptors may modify the intensity and also the direction of a "spontaneous nystagmus," or may even cause its appearance in certain positions of the head.

The experience that in some of the animals nystagmus was present in abnormal positions only seems to suggest that the examination of a patient with a suspected cerebellar lesion should routinely include a test for positional nystagmus. Such an examination may yield positive results when the patient is in certain positions despite the absence of spontaneous nystagmus in the normal position.

DISCUSSION

DR. H. WYCIS: Dr. Spiegel has put me to work on a project that may have practical application in that we are studying alterations in the appearance and amplitude of nystagmus by changing the patient's position. He has demonstrated that in the normal position no nystagmus appears but with a changed position of the whole body and head nystagmoid movements are elicited.

DR. J. C. YASKIN: It has been known for many years that lesions of the cerebellum are not responsible for nystagmus unless they press on the underlying structures of the brain.

DR. ERNEST A. SPIEGEL: I had believed for several years that nystagmus in cerebellar diseases was due either to pressure or to infiltration of the vestibular nuclei by infection of abscess, but after what I have now seen my impression is changed. One must admit that nystagmus may appear also with cerebellar lesions which leave the vestibular nuclei and fiber systems histologically intact. I think much of the controversial attitude of the various authors is due to the fact that the cases were incompletely studied and that the patients were tested in only one position.

Book Reviews

Surgical Diseases of the Spinal Cord, Membranes and Nerve Roots: Symptoms, Diagnosis and Treatment. By Charles A. Elsberg, with chapters by Dr. Cornelius G. Dyke and Dr. Abner Wolf. Price $14. Pp. 598, with 249 illustrations. New York: Paul B. Hoeber, Inc., 1941.

This volume is, in a sense, a new and revised edition of Elsberg's "Diseases of the Spinal Cord" (1916) and "Tumors of the Spinal Cord" (1925). The author has devoted a large part of his lifetime to the subject. After a brief account of pertinent anatomic and physiologic facts, the book discusses lumbar puncture and the information to be derived from it, injuries, congenital abnormalities, inflammations, tumors, diseases of the vertebrae, abnormalities of the blood vessels and the technic of and indications for operation. The discussion of tumors of the spinal cord, nerve roots and membranes occupies six of the seventeen chapters.

The chapters contributed by Dyke and Wolf are detailed, accurate and profusely illustrated, but there is evidence that some of the other chapters have not been so carefully revised. For example, in chapter 4, on injuries of the spinal cord and nerve roots, nothing is said of the comfortable, and now universally adopted, method of caliper extension for fractures of the cervical vertebrae. In the localization of thoracic lesions the useful and easily elicited Beevor sign is not mentioned. The positions assumed by the upper limbs in cervical fractures, long ago pointed out by Thorburn in his classic study, are not mentioned. One has occasion to deplore the tendency, prevalent now in nearly all writing on neurologic subjects, to use "dura" for "dura mater," "medulla" for "bulb," etc. One might mention also the erroneous placing of accents in the name of the great French neurologist Dejerine. The book is also not free from the general practice, derived from the German medical literature, of using complicated phrases as nouns. But the reviewer has some hesitation in pointing out these minor oversights and defects in a book of such general excellence.

The information given in the book is accurate and the advice sound and conservative, as one might expect from the extensive experience of the author. The style of the writing is, in general, clear and readable. The printing is excellent and singularly free from typographic errors; the only defect noted by the reviewer was one illustration upside down. The book is a worthy addition to American neurologic literature and is heartily recommended to members of the medical profession.